Factors influencing QTc interval prolongation during kidney transplantation

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Summary

Background: During renal transplantation, factors causing disturbances of the repolarization process, defined by the QT interval, may lead to ventricular arrhythmias. The aim of this study was to determine a relationship between QT interval prolongation and metabolic homeostasis, and durations of cold ischemia time (CIT) and warm ischemia time (WIT) during renal transplantation.

Material/Methods: From among 198 consecutive renal transplant patients, 68 (mean age 45±12 years) were included in a prospective observational pilot study. Prior to the procedure, arterial blood gas analysis was performed, and digital Holter ECG monitoring was applied and continued for 12 hours. Subsequent arterial blood gas analysis was performed 30 minutes after graft reperfusion.

Results: QTc changed dynamically and significantly during the perioperative period. Ventricular arrhythmias were observed only during graft reperfusion. Recordings showed that 33 out of 68 patients had ventricular extrasystoles, and non-sustained ventricular tachycardia was observed in 2 patients. No patients presented with hemodynamic instability. There was no statistical correlation between CIT or WIT and the difference (delta) between the final and initial values of the pH, potassium and lactate levels, QTc range, maximal QTc or QTc measured at the predefined time points.

Conclusions: The renal transplantation procedure carries a high risk of ventricular repolarization period disturbances that can lead to life-threatening tachyarrhythmias despite optimal hemodynamic or metabolic status and independent of CIT and WIT.

Key words: kidney clinical • holter electrocardiography • QT interval • renal transplantation


Word count: 2362
Tables: 2
Figures: 4
References: 14

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**Background**

The wide use of dialysis has led to a significant increase in survival rates of patients with chronic renal failure. However, dialysis is still only a bridge to the definitive treatment, which is renal transplantation. Stability during the transplantation procedure is of crucial importance, especially after the time of reperfusion, which is critical for early graft function [1]. During renal transplantation and in the early postoperative period, the myocardium is influenced by many factors that are potentially pro-arrhythmic – drugs, hemodynamic disturbances, metabolic disturbances, and procedure-related factors [2-4]. Patients with end-stage renal disease, due to renal insufficiency *per se* and due to hemodialysis treatment, suffer from acute and chronic electrolyte disorders and acid-base disorders, which can induce repolarisation changes measured by the corrected QT interval (QTc) [5-7]. The risk of development of fatal cardiac arrhythmias is directly proportional to the degree of QTc prolongation [8,9]. Factors leading to disturbances of the repolarisation time may potentially be the cause of ventricular arrhythmias, resulting in cardiac episodes such as syncope, cardiac arrest, or sudden cardiac death [10,11]. The pattern of cardiovascular disease in patients with chronic renal failure differs from the general population, having a disproportionate increase in the incidence of sudden cardiac death rather than myocardial infarction. Therefore, diagnosis of factors influencing QTc prolongation in kidney recipients in the periparative period may be of critical importance.

The aim of our study was to determine the relationship between QT interval prolongation and metabolic homoeostasis, and the durations of cold ischemia time (CIT) and warm ischemia time (WIT) during renal transplantation.

**Material and Methods**

A prospective observational pilot study was conducted from September 2008 to October 2010 in the Department of Anesthesia and Intensive Care of the Pomeranian Medical University (PMU) in Szczecin, Poland. The protocol was approved by the Ethics Committee of the Pomeranian Medical University (BN-001/66/08), and all patients gave written, informed consent prior to enrollment in the study. All patients who had renal transplant procedures performed in the General Surgery and Transplant Department of the PMU during the study period were screened for inclusion in the study. From among 198 patients undergoing renal transplant during this period, only 68 patients met the inclusion criteria. The exclusion criteria were: medications prolonging QT interval, sustained atrial fibrillation, implantable pacemaker or cardioverter-defibrillator, severe cardiac pathology in the preoperative echo study (systolic or diastolic dysfunction, hypertrophic and dilated cardiomyopathy), and history of myocardial infarction. A group of 68 adult Caucasian patients, with a mean age of 45±12 years (20-66), 41 males and 27 females, who underwent their first kidney transplantation, were included in the study. All patients were hemodialyzed immediately prior to the transplant procedure. The preparation prior to the transplant procedure consisted of the administration of immunosuppressive agents, according to local protocol, consisting of mycophenolate mofetil, tacrolimus and methylprednisolone. All patients in our study group received grafts from deceased organ donors (mean donor age 43±7 years). The organs were stored in Euro Collins solution ( Fresenius Kabi GmbH), for a maximum storage time of 48 hours. A right iliac incision was performed to expose the retroperitoneal space, the end of the renal vessels was connected with the side of the external iliac vessels, and the ureter was connected to the urinary bladder using the supravesicular technique without the anti-reflux method. Just prior to the graft reperfusion, 500 mg methylprednisolone was administered intravenously (Figure 1).

Perioperative monitoring consisted of invasive blood pressure measurement and central venous pressure measurement. Patients underwent general anesthesia (GA), using local protocol, including fentanyl, propofol and cis-atracurium infusion on induction of GA, sevoflurane for maintenance of anesthesia, and paracetamol and morphine IV or IM as per acute pain treatment protocol.

Perioperative hemodynamic targets were used to maintain blood pressure, heart rate and central venous pressure within normal ranges using colloids, colloids and catecholamines infusions (if needed) following local protocol. Additional patient monitoring during the procedure and in the postoperative period consisted of a continuous ECG tracing for 12 hours postoperatively (digital Holter ECG monitor type 300-7 Suprima system, Oxford, UK). There were 7 electrodes placed in standard position type B, which generated ECG tracing in 3 leads: channel 1 – lead CM-5 (V5), channel 2 – lead CS-1 (V1), channel 3 – lead IS (III), standard amplification of 1 mV/cm and...
speed of 25 mm/s. After manual trace analysis and arrhythmia classification, automated interval measurement was performed (including QT interval corrected according to Bazett’s formula via automated interpretation: QTc interval = QT/RR^{1/2}). Sinus rhythm disturbances were classified as: ventricular and supraventricular extrasystoles and tachyarrhythmias, atrioventricular blocks and pauses of more than 2.5 seconds.

Metabolic monitoring consisted of electrolytes and arterial blood gas analysis prior to anesthesia induction and at 30 minutes after reperfusion. The following parameters were analyzed: pH, pO\textsubscript{2} (partial pressure of oxygen), pCO\textsubscript{2} (partial pressure of carbon dioxide) HCO\textsubscript{3} (bicarbonate ions), BE (base excess), lactate, hemoglobin, hematocrit, K\textsuperscript{+} (potassium ions) and Na\textsuperscript{+} (sodium ions) using a Blood Gas/Electrolyte Analyzer GEM Premier3000 (Instrumentation Laboratory, USA). Hypokalemia was defined as serum potassium ≤3.5 mEq/L, hyperkalemia ≥5.5 mEq/L.

Electrophysiological parameters (rhythm disturbances, variation in the QT interval) were analyzed depending on the metabolic parameters, and the length of CIT and WIT. The above parameters were analyzed at 10-, 20- and 30-minute intervals after the beginning of the operation, at 1-minute intervals after graft reperfusion for the first 10 minutes, at 30-minute intervals after graft reperfusion, and hourly for the next 12 hours. After 12 hours the monitoring was discontinued and the trace analysis was carried out within the next 24 hours by a single observer.

The parametric (paired and unpaired Student’s T tests) and non-parametric tests (Mann-Whitney) were used for comparison between the groups. The correlations between 2 variables were calculated with the Spearman test. All statistical analyses were performed using STATISTICA (StatSoft, Inc., version 8.0). P-values <0.05 were considered statistically significant.

Results

The causes of end-stage renal disease in the study group were as follows: polycystic kidney disease 34%, chronic pyelonephritis 2%, IgA nephropathy 8%, focal segmental glomerulosclerosis 42%, unknown 14%. Mean hemodialysis time prior to the transplantation was 3 years ±1 year. The co-morbidities were: 6/68 (8%) of patients had stable ischemic heart disease (IHD), all 68/68 patients had hypertension (well-controlled by ACE-inhibitors, calcium blockers or angiotensin-receptor blockers), and diabetes in 7/68 (9%) of patients. No patients were treated by a B-blocker, and none were diagnosed with severe heart failure or symptomatic generalized atherosclerosis.

All patients underwent a 3-hour dialysis within the 5 hours preparation time prior to the transplant procedure; their metabolic parameters were within normal limits (Table 1).

Mean transplant procedure time was 123±28 minutes. In the study group the mean cold ischemia time (CIT) was 18.6±8.9 (6–36) hours and warm ischemia time (WIT) was 23±6.5 (12–40) minutes.

The value of QTc changed dynamically during the perioperative period. The mean QTc values at the 10\textsuperscript{th}, 20\textsuperscript{th} and 30\textsuperscript{th} minute after the beginning of the procedure were: 466±24, 467±24, 467±25 ms, respectively. The mean delta QTc value during the 12 hours of the observation period was 45±18ms (range 16–117ms), with its abnormal lengthening (above 60 ms) being observed in 10 patients. The prolongation of the QTc value at the consecutive observation points was statistically significant (Table 2).

The mean heart rate during the 12-hour recording was 81±11 beats per minute (57–104). Ventricular arrhythmias, such as ventricular extrasystoles (VES) or ventricular bigeminies, as well as episodes of transient ventricular tachycardia
were observed only during graft reperfusion. The recordings showed that 33 out of 68 patients had ventricular extrasystoles (mean number of VES was 64±164 [1–704]), and for 4 patients the number of VES was more than 200 episodes during 12 hours. Non-sustained ventricular tachycardia was observed in 2 patients (duration time of arrhythmia was 10 and 16 seconds), without any significant circulatory, metabolic or electrolyte disturbances at that time. In these cases, initially QTc was 436 and 473 ms, maximum QTc 489 and 510 ms, CIT was 19 and 25 hours, WIT 10 and 11 minutes, respectively, in the absence of any metabolic or electrolytes changes. There was no difference in WIT between patients with less than 200 VES/12 hours and more than 200 VES/12 hours. No significant supraventricular arrhythmias, bradycardia, pauses or atrioventricular blocks were noted during the observation period.

The mean QTc interval was initially 464±25 ms, with its post-reperfusion lengthening to maximal values of 498±19 (430–559) ms, and gradual decrease during the first few hours to initial values towards the end of the observation period. The dynamics of QTc interval length depended on the observation period (Figure 2).

During the operation the mean systolic blood pressure amplitude was 74±19 and the mean diastolic blood pressure amplitude was 30±8 mmHg. None of the patients had perioperative hemorrhage requiring red blood cells transfusion. The mean blood loss was 226 ±100 mls. No patient presented with hemodynamic instability during renal transplantation and no catecholamine infusion was needed.

There was no statistical correlation between CIT or WIT and the difference (delta) between the

| Table 1. Haemodynamic and metabolic correction prior to and during the procedure. |
|---------------------------------------------|---------------------------------------------|-----------------|
| **Prior to transplant**                     | **30 min after cross-lamp release**         | **p**           |
| SBP [mmHg]                                  | 123±22                                      | 133±18          | 0.0002          |
| DBP [mmHg]                                  | 72±12                                       | 77±18           | 0.0217          |
| pH                                          | 7.36±0.04                                   | 7.33±0.03       | <0.001          |
| pO₂ [mmHg]                                  | 128±12                                      | 129±12          | NS              |
| pCO₂ [mmHg]                                 | 43±5                                        | 45±4            | <0.0001         |
| BE [mmol/L]                                 | 0±2.5                                       | −1.4±2.4        | <0.0001         |
| HCO₃⁻ [mmol/L]                              | 25±2                                        | 24±3            | 0.0003          |
| Hemoglobin [g/dl]                           | 11.3±1.8                                    | 11.2±1.7        | NS              |
| Haematocrit [%]                             | 36±5                                        | 36±5            | NS              |
| Lactate [mmol/L]                            | 0.8±0.4                                     | 0.9±0.3         | 0.0008          |
| Na⁺ [mmol/L]                                | 134±2.4                                     | 134±2.3         | NS              |
| K⁺ [mmol/L]                                 | 4.4±0.6                                     | 4.8±0.7         | <0.0001         |

SBP — systolic blood pressure; DBP — diastolic blood pressure; pO₂ — partial pressure of oxygen; pCO₂ — partial pressure of carbon dioxide; BE — base excess; HCO₃⁻ — carbonic ion; Na⁺ — sodium ion; K⁺ — potassium ion; NS — not significant.

| Table 2. Statistical significance of QTc values in predefined time points. |
|---------------------------------------------|---------------------------------------------|-----------------|
| **Predefined time points**                 | **Prior to transplant**                     | **p**           |
| Mean QTc±SD [ms]                           | Mean QTc±SD [ms]                            |                 |
| 10 minutes after the beginning of the operation | 466±24                                      | 464±25          | p=0.001         |
| 20 minutes after the beginning of the operation | 467±24                                      | 464±25          | p<0.0001        |
| 30 minutes after the beginning of the operation | 467±24                                      | 464±25          | p<0.0001        |
| 1st minute after cross-lamp release        | 481±20                                      | 464±25          | p<0.0001        |
| 10th minute after cross-lamp release       | 483±19                                      | 464±25          | p<0.0001        |
| 30th minute after cross-lamp release       | 474±17                                      | 464±25          | p<0.00015       |

The mean QTc interval was initially 464±25 ms, with its post-reperfusion lengthening to maximal values of 498±19 (430–559) ms, and gradual decrease during the first few hours to initial values towards the end of the observation period. The dynamics of QTc interval length depended on the observation period (Figure 2).
final and initial values of the pH, potassium level and lactate level, and systolic or diastolic blood pressure. There was no statistical correlation between CIT or WIT and the QTc range (defined as the difference between minimal and maximal QTc values, Figures 3 and 4), as well as for maximal QTc or QTc measured in the time frames (minutes for the first 30 minutes, hourly thereafter) during the 12 hours of the observation period.

**DISCUSSION**

Hemodynamic stability during the kidney transplant procedure and during most of the period after the graft reperfusion is of crucial importance for early graft function. Normal QT interval is an index of normal ventricular repolarisation. Concomitant diseases (e.g., myocardial infarction, heart failure, disseminated atherosclerosis) add to the acquired increase of the QTc interval, increasing the risk of sudden cardiac death due to dysrhythmias. Even sudden, transient and short-lived QTc prolongation may lead to life-threatening dysrhythmias and death. Multiple perioperative factors (anesthetic technique, operative technique, drugs, the time immediately post-dialysis) directly influence the rapid QTc interval changes [1,3]. Using Holter monitoring, the prolongation of QTc interval is reported in 30% of transplant recipients and 70% of patients with chronic renal failure [7,10]. Patient optimization prior to the transplant procedure with maximum metabolic homeostasis and hemodynamic stabilization during the entire perioperative period are factors necessary for the reduction of risk associated with the procedure [9].

The purpose of this study was to search for a relationship between arrhythmias (with QTc interval lengthening as one of the initiating factors) and the transplant procedure. In our study group the QTc interval fluctuated dynamically during the transplant procedure. Independent of the initial value of QTc after dialysis and prior to the transplant operation, an increase of QTc values after graft reperfusion was noted. Maximal values of QTc were most commonly visible in the 7th minute post-reperfusion. Consecutive minutes have shown that the QTc values were decreasing to the initial values approximately 5–6 hours after the transplant procedure. In the period thereafter, the QTc values were decreasing to the values prior to the operations, a phenomenon that can be explained by the hemodialysis effect or the influence of immunosupression on the length of QT interval. The strength of this study is its very homogenous group of patients who underwent the same procedure, performed by a single surgeon – homogeneity that was based on the restrictive protocol and the fact that all patients had hemodialysis prior to the transplant, the same immunosupression protocol was applied, and the study included only the patients with the least cardiac co-morbidity and only hemodynamically and metabolically stable patients.
The logical approach is for the surgical team to maximally shorten the warm and cold ischemia times, which could lead to better patient outcome and less cardiovascular instability. After eliminating all of the known factors prolonging the QT interval (initial hypokalemia, heart failure, and drugs influencing the QT value), we analyzed whether the length of cold or warm ischemia time, acid-base equilibrium changes or potassium levels during the procedure influence the length of the QT interval and predispose to ventricular arrhythmias. This study demonstrated that neither CIT nor WIT were factors significantly influencing the prolongation of QTc or its delta increase during the procedure and within the 12 hours of observation afterwards. It can be proof of the good quality of the kidney preserving fluid used, but the necessity of maximal CIT reduction is well known. It can only be hypothesized that there may be some metabolites generated, apart from lactates (which were not elevated in our study group), that may additionally influence the repolarisation phase of the cardiac cycle leading to ventricular arrhythmias.

One assumes that optimal hemodynamic or metabolic status in terms of electrolyte and blood gas balance translates into patient safety during and after renal transplantation [1,6,12–14]. The fact that acidosis and accumulation of lactates can lead to disturbances of the repolarization period has been established in many papers in the recent literature. Our study shows that the risk of ventricular arrhythmias (determined by Holter monitoring of QTc interval) can be a potential problem despite careful patient optimization during the perioperative period. Despite the lack of statistical significance of the results, 2 patients experienced 2 episodes of non-sustained ventricular tachycardia (registered in the period directly after graft reperfusion). One of these patients had QTc prolonged above 450 ms during the entire observation period. The second patient had a normal QTc value prior to the operation, but immediately after graft reperfusion it was pathologically prolonged. Neither of these 2 cases can be explained by electrolyte or metabolic abnormalities. The question of whether cold ischemia time (19 and 25 hours) influenced the pathological QTc lengthening remains open; the answer is most likely multifactorial.

**CONCLUSIONS**

This pilot study underlines the necessity of postoperative monitoring based not only on standard methods, but also using more advanced means of enabling the rapid correction of disturbances to avoid postoperative non-surgical complications, including sudden cardiac death. The renal transplantation procedure carries a high risk of ventricular repolarisation period disturbances, which can lead to life-threatening tachyarrhythmias despite optimal hemodynamic or metabolic status. Further research is necessary to generate recommendations improving the standards of perioperative care of renal transplant recipients.

**REFERENCES:**
