HRV Influence During Renal Transplantation Procedure on Long-Term Mortality

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ABSTRACT

Background. The autonomic nervous system plays an important role in heart function regulation. One of the most acknowledged methods for noninvasive measurement of autonomic system activity is to determine heart rate variability (HRV). Reduced HRV parameters—heart rate rigidity/stiffness—are an independent prognostic factor of sudden cardiac death risk because of arrhythmia. Renal transplantation is an important factor in HRV changes because of hemodynamic and ion disturbances. The main purpose of this study was to determine the influence of HRV disturbances during renal transplantation procedures on long-term mortality in patients with chronic kidney disease.

Methods. A prospective observation study was performed in the Department of Anesthesiology, Intensive Care, and Acute Poisoning, Pomeranian Medical University, Szczecin, Poland. There were 75 patients (mean age, 47 $\pm$ 12 years; 42 men) treated with renal transplantation between 2008 and 2010. Patients were monitored with electrocardiographic tracing with the use of 7 electrodes in position type B. The final stage of analysis was to determine the possible relationship between HRV parameters during the perioperative period and the number of deaths within a 5-year follow-up.

Results. HRV parameters during the perioperative period of renal transplantation and the number of deaths within a 5-year follow-up, measured by use of the Holter method, did not differ among patients in the studied population.

Conclusions. HRV is a noninvasive and confirmed tool used for the evaluation of autonomic function and mortality risk in patients with end-stage renal disease. HRV parameters recorded in the perioperative period are not optimal stratification tools for estimating the risk of cardiac deaths in patients with end-stage renal disease.

PATHOLOGICAL sympathetic nervous system activation plays an important role in the mechanism of many diseases (hypertension, ischemic heart disease, congestive heart failure, sudden cardiac death, and cardiorenal syndrome). Many studies have reported on enhanced sensitivity to norepinephrine and the increased plasma concentration of catecholamines in these cases [1–3]. On the other hand, chronic sympathetic nervous system overactivity may lead to the development of hypertension and cardiovascular disease in the group of patients with end-stage chronic kidney disease (CKD) treated with hemodialysis. This phenomenon is explained by the compensatory role of the sympathetic nervous system caused by acute changes of fluid and the electrolyte balance during hemodialysis.

Direct methods of assessment of sympathetic nervous system activity are often not available in the clinical context. Therefore, in many studies, noninvasive techniques were used. Heart rate variability (HRV), baroreceptor sensitivity, and blood pressure variability are the most popular methods. HRV refers to the beat-to-beat alterations in the

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heart rate with the use of time domain and spectral domain methods. Under resting conditions, the electrocardiogram (ECG) of healthy individuals exhibits periodic variations in R-R intervals. This rhythmic phenomenon, known as respiratory sinus arrhythmia, fluctuates with the phase of respiration—acceleration during inspiration, and deceleration during expiration. Spectral analysis of heart rate oscillations allows the identification of a low-frequency (LF) component (related to sympathetic and vagal outflows) and a high-frequency (HF) component (related to respiration). The LF/HF ratio is frequently used as an index of sympathovagal interaction.

Reduced HRV is used as a marker of reduced autonomic activity. HRV assessment is also used as a clinical tool for the stratification of the increased risk of cardiac mortality, because decreased global HRV is found to be a strong predictor of increased all-cause cardiac and/or arrhythmic mortality and morbidity in CKD patients. In patients with end-stage renal disease (ESRD) treated with hemodialysis, HRV is markedly suppressed; there is an increase in LF/HF ratio, and lower SDNN and LF and HF values are usually observed.

The procedure of renal transplantation is an important factor of HRV changes caused by hemodynamic and ion disturbances induced by perioperative stress and drugs. Successful renal transplantation is associated with improvement of chronic sympathetic overactivity through the correction of electrolytes and fluid and hormone homeostasis. However, the time of normalization of sympathetic nervous system activity is controversial (assessed more than 1 year); this means that the time of increased risk of cardiac mortality after renal transplantation is also unknown. The influence of HRV disturbances during renal transplantation and 24 hours after the procedure on long-term mortality as a risk stratification tool has not been assessed in the available literature.

The main purpose of this study was an assessment of the influence of HRV disturbances during renal transplantation procedures on long-term mortality in CKD patients.

METHODS

The study was performed in accordance with the Declaration of Helsinki for Human Research. The study protocol was approved by the local ethics committee. A prospective, observational study was performed in the Department of Anesthesiology, Intensive Care, and Acute Poisoning, Teaching Hospital No. 2, Pomeranian Medical University, Szczecin, Poland. There were 75 patients (mean age, 47 ± 12 years; 42 men) treated with renal transplantation between the years 2008 and 2010 included in the study. Patients with atrial fibrillation, ventricular premature beats, atrioventricular blocks, implanted pacemakers, and with diabetes were excluded from the study. All patients qualified for the study underwent general anesthesia in the same protocol (fentanyl, propofol, cisatracurium for the induction and fentanyl with sevoflurane to maintain anesthesia). In the operating room, standard cardiovascular system monitoring was applied (an ECG, continuous invasive blood pressure monitoring, and central venous pressure monitoring with the use of an Infinity Delta monitor (Draeger G, Telford, USA). Additional patient monitoring was started before the induction of general anesthesia and continued during the procedure and 24 hours after operation; this consisted of continuous ECG tracing (digital Holter ECG monitor type 300-7 Suprima system; Oxford, United Kingdom) with the use of 7 electrodes placed in standard position type B, which generated ECG tracings in 3 leads: V_5, V_1, and III at a speed of 25 mm/s and standard amplification of 1 mV/cm. For HRV measurements, the computer system classified the QRS complexes as normal beats, ectopic beats, and artifacts. This classification was controlled visually and corrected manually when necessary by an experienced physician. After manual trace analysis, we performed arrhythmia classification and HRV assessment (frequency and time domain methods). The following HRV parameters were calculated for each patient to characterize cardiac sympathetic-parasympathetic function: (1) the 24-hour SD of normal R-R intervals (SDNN, ms) as a global measure of HRV; (2) the mean number of times per hour in which the change in successive normal sinus (NN) intervals exceeds 50 ms (pNN50); (3) the square root of the mean of the squared differences between adjacent normal R-R intervals (rMSSD, ms) as time domain parameters. Moreover, LF and HF powers (ms^2) were recorded for the 0.04- to 0.15-Hz and 0.15- to 0.40-Hz bands, respectively, and the ratio of LF to HF power (LF/HF ratio) were calculated.

Metabolic monitoring consisted of electrolytes and arterial blood gas analysis before anesthesia induction and at the end of the procedure. The following parameters were analyzed: pH, hemoglobin, lactate, hematocrit, and potassium ion concentration (K^+), measured by use of GEM Premier 3000 (Instrumentarium Laboratory, United States).

Follow-Up and Outcome Measurements

Follow-up interviews were performed by telephone survey 5 years after surgery to determine mortality and reasons for death. All reported facts were verified by the family or by the review of hospital charts.

The final stage of analysis was an assessment of the possible relation between the HRV parameters recorded during the perioperative time and the numbers of deaths within a 5-year follow-up.

Statistics

All parameters are expressed as mean ± standard deviation. The Fisher exact test was used to determine the statistical significance of differences in rates of occurrence. An unpaired *t* test or Mann-Whitney *U* test was used for comparisons of continuous data between 2 groups. Intra-group comparisons of continuous data were performed by use of a paired *t* test or Wilcoxon signed-rank test. Statistical significance was defined as $P < .05$.

RESULTS

Seventy-five patients (mean age, 47 ± 12 years; 42 men) treated with renal transplantation in the years 2008 to 2010 were included in the study. The main cause of kidney transplantation was end-stage renal failure caused by glomerulonephritis. All of the recipients were treated with chronic dialysis before renal transplantation. The mean time of dialysis in the study population was 3 years ± 1 year. Only 4 of 75 patients were treated with peritoneal dialysis; 47% of patients had arterial hypertension, 8% had coronary disease, and none were diabetic. The clinical and demographic features of the 75 patients who completed the 5-year study did not differ from the analyzed subgroups.