Introduction

The annual cardiovascular mortality of children with chronic renal failure is three order of magnitude higher than that of the general population. The two most frequent causes of dialysed children’s cardiac death are cardiac arrest and arrhythmia.

A number of possible mechanisms have been proposed to explain the excess of cardiovascular mortality including hypertension, anemia, atherosclerosis due to disturbed calcium, phosphate, homocystein and lipid metabolism. Recently, the role of cardiovascular autonomic dysfunction has been emphasized as an independent risk factor of cardiovascular mortality in uremia. Its childhood occurrence, pathomechanism and treatment have not been elucidated yet.

The diagnosis of cardiovascular autonomic dysfunction is based on cardiovascular reflex tests and heart rate variability (HRV).

There is some opposition in the diagnosis of autonomic dysfunction and in its relationship with cardiovascular mortality.

On the basis of reflex tests and HRV the sympathetic activity is low in uremia. However, according to human and animal studies low sympathetic activity should be accompanied with lower incidence of cardiac arrhythmias.

Formerly the high- and the low-frequency heart rate variability were thought to reflect the vagal and the sympathetic activity, respectively. However, recent studies have shown that both of them are directly proportional with vagal and inversely proportional with sympathetic activity.

My aim was to elucidate the childhood occurrence and the pathomechanism of cardiovascular uremic autonomic dysfunction.
Aim

1) To elucidate the childhood occurrence of uremic autonomic dysfunction by measuring cardiovascular reflexes and heart rate variability in predialysed, dialysed and transplanted patients.

2) To elucidate the pathomechanism of uremic autonomic dysfunction

   I. examining the hemodynamic changes during orthostasis in dialysed and transplanted children.

   II. comparing the relationship between heart rate variability and heart rate in children with hypertension, in healthy and uremic children.

   III. examining the role of sympathetic activity in uremic autonomic dysfunction determining the effect of β-adrenergic blockade on heart rate variability in patients with end-stage renal disease.

Methods

The cardiovascular autonomic function was assessed by measuring cardiovascular reflexes and heart rate variability.

Reflex tests

Valsalva and 30/15 heart rate ratio, respiratory sinus arrhythmia induced by hyperventilation, resting heart rate, standing/lying heart rate ratio, blood pressure change secondary to hand grip test and to orthostasis were examined in 10 dialysed and 10 transplanted children and young adults. Stroke volume was measured by impedance cardiography during supine and orthostasis.

Heart rate variability

Fifteen hemodialysed, 16 transplanted, 10 patients with mild uremia (GFR: 15-75 ml/min*1.73m²), 19 patients with hypertension but no uremia, and 25 healthy volunteers were examined. Heart rate variability was examined during supine and head-up tilt (65°).

Effect of propranolol on heart rate variability

The effect of intravenous propranolol on heart rate variability was examined in a randomized, placebo-controlled, double-blind, cross-over study involving 13 children and young adults with end-stage renal disease. The measurements were performed just before hemodialysis treatment, after 30 minutes supine resting period and were completed with echocardiography. Before the injection of placebo or propranolol blood was drawn for plasma catecholamine measurements. (Heim Pál Hospital, HPLC).
Heart rate variability
High (HFV: 0.4-0.15Hz) and low frequency (LFV: 0.15-0.04Hz) heart rate variability were determined. Measurements were performed with Cardiotens-01, a combined blood pressure and Holter-monitor (Meditech Ltd, Budapest). Data were analysed by Medibase 1.35 software (Meditech Ltd).

Impedance cardiography
Stroke volume was determined by impedance cardiography (ICG-M401, ASK Ltd, Budapest). Cardiac output and peripheral resistance were computed.

Ethics
Written informed consent was obtained prior to entry into the studies. The studies conformed to the Helsinki declaration and were approved by the Regional Ethics Committee (TUKEB 25/2000. and 72/2001.).

Statistics
The distribution of the data was examined by Shapiro-Wilk’s W test. Data with normal distribution (and homogeneous variance) were evaluated with ANOVA, ANCOVA, Newman-Keuls post hoc test, Student’s one and two sample t test and Pearson correlation. Data with non-normal distribution (or with heterogeneous variance) were evaluated with Kruskal-Wallis ANOVA, Mann-Whitney, Wilcoxon tests and Spearman correlation. The Mann-Whitney test was evaluated according to Holm’s method. All statistical analysis was performed using Statistica 5.0 software package.

Results

1. Reflex tests
According to the reflex tests, 3 of the 10 dialysed patients had mild and 2 dialysed patients had definite autonomic dysfunction. One of the 10 transplant patients showed mild autonomic dysfunction. Significant difference was found between the dialysed and the transplanted group in 4 reflex tests (hyperventilation, Valsalva ratio, resting heart rate and standing/lying heart rate ratio).
During supine, the stroke volume of dialysed patients was lower than in transplant patients. However, it did not decrease further during orthostasis, thus a relatively small increase of heart rate was enough in dialysed patients to maintain their blood pressure. The low stroke volume can explain the reduced Valsalva and standing/lying heart rate ratio of dialysed patients. The low respiratory sinus arrhythmia secondary to hyperventilation and the high resting heart rate of dialysed patients’ may be the consequences of both autonomic neuropathy and sympathetic overactivity. Thus, the autonomic tests – with the knowledge of the different hemodynamics of dialysed patients – are not specific in diagnosing neuropathy as a cause of uremic autonomic dysfunction.

2. Heart rate variability
Heart rate variability (HRV) of dialysed patients was lower than that of controls. The HRV of transplanted and dialysed patients was similar, and statistically was not different from that of the control group. Heart rate variability of patients with hypertension but no uremia and that of control subjects during orthostasis was similar to
that of dialysed patients. It showed that sympathetic overactivity itself can reduce heart rate variability to a similar extent as uremia.

There was a strong, negative linear correlation between heart rate and high-frequency heart rate variability (HFV) in all groups. The HFV after its correction for heart rate was normal in patients with hypertension, in mild uremic, in transplant and in dialysed patients with preserved diuresis. It led to the suggestion that the reduction of HRV in chronic renal failure is partly due to sympathetic overactivity. The HFV of anuric dialysed patients remained low even after its correction for heart rate.

3. **Effect of propranolol on heart rate variability**

Heart rate variability of patients with end-stage renal disease increased secondary to propranolol. The extent of the increase correlated negatively with the plasma dopamine level and positively with the residual urine volume. The increase of heart rate variability – in patients without previous β-blocker treatment – was proportional to the reduction of heart rate. The plasma dopamine level was elevated in all but one patient. Six patients (46%) had an elevated plasma norepinephrine- (4) and/or epinephrine-concentration (4). These results confirmed that the reduction of HRV proportional with the increase of heart rate is at least partly the result of sympathetic overactivity. It showed that diagnosing autonomic neuropathy by the single measurement of HRV is not reliable. However, the HRV of patients with end-stage renal disease was not normalized by propranolol, therefore the role of uremic autonomic neuropathy in the reduction of HRV cannot be excluded.

**Thesis**

1. The autonomic function of children with chronic renal failure was examined as first in the literature. On the basis of the reflex tests and the measurement of heart rate variability, it has been concluded that the autonomic dysfunction can be detected already in childhood uremia. The autonomic function of transplanted children and young adults – similarly to the adults’ literary data – is markedly better, thus the uremic autonomic dysfunction is reversible.

2. With the knowledge of the hemodynamics of dialysed patients it has been concluded that the abnormal cardiovascular reflex tests are not specific for diagnosing uremic autonomic neuropathy.

3. By comparing the relationship between heart rate and heart rate variability in patients with hypertension, in healthy and uremic subjects it has been concluded that the reduction of heart rate variability in patients with chronic renal failure is due to their tachycardia to a large extent. Role of sympathetic overactivity in its pathomechanism has been suggested.

4. On the basis of the effect of ?-adrenergic blockade on HRV it has been concluded that the reduction of heart rate variability proportional with the increase of heart rate reflects sympathetic overactivity instead of neuropathy.
5. It has been concluded that the single measurement of heart rate variability is not specific for diagnosing autonomic neuropathy, because HRV is also influenced by altered sympathovagal balance. To examine the effect of autonomic neuropathy, HRV has been adjusted for HR.

6. Since HRV of anuric patients remained low even after its adjustment for heart rate, the role of uremic autonomic neuropathy in the generation of low heart rate variability cannot be excluded.

**Theoretical and practical benefit**
The beneficial effect of a sympatholytic agent on heart rate variability in end-stage renal disease has been presented as first. These results can contribute to the understanding of the pathomechanism of uremic autonomic dysfunction, to the establishment of a rational therapy and to further prospective clinical investigations evaluating the effect of sympatholytics on cardiac mortality in end-stage renal disease.

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Publications related to the thesis


4. **Tory K** Horváth E, Süveges Zs, Bokor É, Sallay P, Berta K, Szabó A, Tulassay T, Reusz GS. Autonomic dysfunction in uremia assessed by heart rate variability. *Pediatr Nephrol* (accepted for publication) IF: 1.42


Book chapter:


Publications not related to the thesis

1. Rohács T, **Tory K** Dobos A, Spáť A. Intracellular calcium release is more efficient than calcium influx in stimulating mitochondrial NAD(P)H formation in adrenal glomerulosa cells. *Biochem J* 1997;328:525-8; IF: 3.579


Abstracts related to the thesis


5. **Tory K** Süveges Zs, Sallay P, Reusz GS. Vagal tone in uremic children and young adults studied by heart rate variability. *Monatsschr Kinderh* 2001;149(Suppl 2):S1192, IF: 0.134


10. **Tory K** Süveges Zs, Sallay P, Berta K, Szabó A, Tulassay T, Reusz GS. A new parameter designed to differentiate the effect of autonomic neuropathy from that of sympathetic overactivity on heart rate variability in hemodialysis patients. *Nephrol Dial Transplant* 2003;18(S3):P T792, IF: 2.57