MAPS OF VENTRICULAR ACTIVATION TIME (VAT) DIFFERENCES IN CHILDREN ON PERITONEAL DIALYSIS — A PILOT STUDY

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◆ **Background:** Decrement of glomerular filtration rate leads to many serious complications that cause both functional and structural impairments of the other organs. Long-term clinical observations of children and teenagers with end-stage renal disease (ESRD) showed that more than one third of those patients manifested various cardio-vascular conditions. The aim of the study was to analyze possible disturbances in the heart ventricular conduction system by using a technique of ventricular activation time (VAT) differences in ESRF children on peritoneal dialysis (PD) with normal electrocardiogram (ECG) examinations.

◆ **Material and methods:** The study group comprised 10 ESRD children (mean age: 13.6 ± 2.31 years) on peritoneal dialysis – group I. The control group (group II) consisted of 26 age-matched healthy children with no clinical evidence of renal or cardiac disease and with normal 12-lead ECG recordings. Each of the ESRD patients was also subjected to the standard ECG examination. In order to capture possible heart conduction abnormalities, body surface potential mapping (BSPM) recordings were performed in PD patients between the successive dwells ('on empty abdomen') with a HPM-7100 Fukuda Denshi system. Based on the source ECG data, the original technique of a VAT difference map was then applied.

◆ **Results:** Differences between VAT values for the two examined groups of children, controls and ESRD patients on PD, were significantly pronounced in the region of the right upper anterior thorax, the entire left thorax and nearly in the total back. Such a pattern of VAT delays indicates a pathological electric transmission in the intra-ventricular conduction system of the left anterior fascicle of His bundle.

◆ **Conclusion:** 1. VAT maps (isochrone maps) can be useful to detect abnormal spreading and depolarization through

the heart ventricles. 2. Map of VAT value differences makes it possible to identify early disturbances in the left His bundle branch in ESRD children treated with peritoneal dialysis regardless of normal 12-lead ECG. 3. Further studies on a larger group of children with ESRD on PD are required to verify the preliminary observations presented herein.

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Chronic kidney disease (CKD) leads to multi-organ disorders, of which cardiovascular complications may be perceived as the most significant, being the main cause of mortality in all patients with CKD. It is estimated that a risk of fatal outcome in children with end-stage renal disease (ESRD) is 10 times higher than that in the general population of children (1,2).

Changes in the circulatory system occur relatively early, at the 2nd stage of CKD, without evident clinical symptoms, however. Most endangered are children with ESRD on chronic dialysis, regardless of applied method (3). Causes of cardiovascular mortality are different in children than in adults, not only because of age difference but also due to dissimilar factors leading to CKD. In children, sudden cardiac arrest and arrhythmia rank first, while cardiomyopathy is the second cause of death. In recommendations on reducing cardiovascular risk in the pediatric population, the American Heart Association placed children with CKD in the group with the highest risk (4).

The pathogenesis of cardiovascular complications in a CKD course is complex and multifactorial (5,6,7,8), consequences of which include vascular changes, degeneration of cardiomyocytes, left ventricle hypertrophy, arrhythmia and disturbances in the heart conduction

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system. The heart conduction system is responsible for electric impulses' normal spreading, starting from the atrioventricular junction through the His bundle and its right and left branches. Changes in His bundle branches lead to ventricular depolarization delays resulting in hemodynamic dyssynchrony. Disturbances in cardiac systolic and diastolic functions, particularly of the left ventricle, are observed in all CKD stages and also after kidney transplantation.

Therefore, it is of utmost importance to identify cardiovascular disorders in CKD patients as early as possible. One of the methods that allows for non-invasive evaluation of changes in the cardiac electric field is body surface potential mapping (BSPM), offering multielectrode recordings from extensive areas of the thorax. Three types of "heart maps" can be obtained with the BSPM system: isopotential, isointegral and isochrones (9).

Isochrone maps, named also VAT (ventricular activation time) maps, precisely depict a progression of electric activation of the heart ventricles in the form of isochrone lines connecting the ventricle sites activated at the same time. We showed previously that VAT maps identify ventricular conduction disorders in children with CKD much earlier than standard 12-lead electrocardiogram (ECG) (10).

The aim of this pilot study was to assess the usefulness of VAT maps to detect disorders of ventricular conduction in PD patients. We hypothesized that there are possible disturbances in the heart ventricular conduction system in children on peritoneal dialysis (PD) that could be detected using an original technique of 'VAT differences map'.

It should be emphasized that, referring to the literature sources, such a study using the above-mentioned method in children with ESRF subjected to PD, has not yet been reported.

MATERIAL AND METHODS

The study involved 10 ESRD children (4 boys and 6 girls; the mean age: 13.6 ± 2.31 years) treated with peritoneal dialysis (PD) – group I. Inclusion criteria were: age above 8 years because of the BSPM electrode dimensions, PD as the first and the only method of ESRD treatment, at least 6-month dialysis, normal (controlled) blood pressure (RR), normovolemia, lack of infection. ESRD children who did not fulfil these criteria were excluded from the study.

The control group (group II) consisted of 26 healthy children (12 boys and 14 girls) at similar age and presenting no renal or cardiac clinical symptoms, as well as showing normal arterial blood pressure values and

no abnormalities on ECG, echocardiography (ECHO) or BSPM examinations.

Causes of chronic kidney disease in the studied population included: chronic glomerulonephritis (6 patients), chronic pyelonephritis (3 patients) and congenital malformations of the urinary system (1 patient).

Time period of renal replacement therapy by automated peritoneal dialysis (APD) varied from 6 months to 1.7 years (mean value: 1.17 ± 0.33 years). The Kt/V index was 2.11 ± 0.05 . Standard prescription of APD (HomeChoice Pro; Baxter Healthcare, Deerfield, IL, USA) included dwell changes of 9 – 12 hours, with 800 – 1,000 mL/m² body surface area (BSA) of 1.36% glucose PD4 (Baxter) per dwell/per fill volume. Two patients had a routine APD prescription. Three patients had PD with physioneal on alternate days; in those patients, VAT maps were taken on the day without physioneal. Five patients had APD cycles with 1.36% PD at night and, additionally, up to 2 continuous ambulatory PD (CAPD) changes during daytime with 2.27% glucose. Glucose concentrations were dependent on fluid amounts to be removed to maintain a clinically euvolemic state. Three children with APD were anuric. The other seven patients with residual renal function had urine output of 721 ± 133 mL/day.

Administered pharmacotherapy included: hypotensive agents, erythropoietin, analogues of vitamin D, vitamin C, folic acid and iron supplements.

Six ESRD patients were treated with antihypertensive drugs (calcium channel blockers, angiotensin converting enzyme inhibitors (ACEI), beta-blocker agents). Three patients were treated with monotherapy (calcium channel blockers or ACEI) and the remaining three with combined therapy (calcium channel blockers with beta blockers or calcium channel blockers with ACEI).

In all patients, serum concentrations of the following substances were assayed: inorganic phosphate (P_i), total calcium (t-Ca), sodium (Na), urea, creatinine (cr), intact parathormone (iPTH), C-reactive protein (CRP) and albumin.

Serum P_i , Na and t-Ca levels were tested by the direct potentiometry method, using ionoselective ISE electrodes by a Konelab automatic analyzer (bioMérieux, Craaponne, France) with the following normal ranges – t-Ca: 8.80 – 10.80 mg/dL; P_i : 4.5 – 5.52 mg/dL; Na: 135 – 146 mmol/L. Serum creatinine was determined by the Jaffe method (normal range: 0.3 – 1.0 mg/dL) and urea was determined by the enzymatic-colorimetric method (normal range: 10.00 – 45.00 mg/dL). Intact parathormone (iPTH) was assayed by the immunoenzymatic method (ELISA; Roche Diagnostics Polska, Warsaw, Poland – normal value: 11.00 – 67.00 pg/mL). Serum albumin was assayed by the Bromocresol Green Dye-Binding Method (normal range: 3.4–4.2 g/dL).

ESRD children were kept on a phosphate-poor diet (phosphate intake < 500 – 800 mg/day) and were treated with compounds binding phosphate in the intestine (calcium carbonate < 35 – 200 mg/kg/day) in order to maintain the serum phosphate concentration between 4.5 – 5.52 mg/dL. Dietary calcium intake was defined as 500 – 600 mg of elementary calcium per day to keep serum calcium concentration between 8.8 – 10.8 mg/dL.

Blood pressure levels were taken after completion of the night dialysis, according to the recommendations (11). The obtained RR results were assessed based on percentile charts in relation to gender, age and body height.

Morning blood samples were collected from the antecubital vein of the PD patients and controls in sitting position, both groups in fasting condition.

ECG AND ECHO

Standard 12-lead ECG examination was performed twice in each examined child. ECG tracings were interpreted, according to commonly accepted criteria (12).

In all ESRF patients, trans-chest ECHO examination was done on the same day as VAT maps recordings with Hewlett-Packard Sonos 1000 apparatus (Hewlett-Packard, Palo Alto, CA, USA), according to the American Society of Echocardiography guidelines. M-mode measurements of the left ventricle (end-diastolic dimension, LVED; interventricular septal thickness and posterior wall thickness) were taken. Left ventricular mass (LVM) was calculated in all patients using the Devereux formula (13). Furthermore, the left ventricular mass index (LVMI) was calculated, according to the de Simone formula ($LVMI = LVM / height^{2.7}$) (14). A cut-off for left ventricular hypertrophy were LVMI values above the 95th percentile, taking into account the age-specific referential values for normal children published by Khoury *et al.* (15).

BODY SURFACE POTENTIAL MAPPING

Body surface maps were obtained from 87-lead Fukuda Denshi HPM-7100 system (Fukuda Denshi Co., Ltd, Tokyo, Japan), in which electrodes are placed at assigned sites on anterior and posterior thorax using disposable tape with the patient in recumbent position. Body surface potential mapping (BSPM) allows for synchronic recording of the heart electric signals from the multielectrode system that are then plotted as various kinds of map (9,10). BSPM recordings were performed in PD patients between the successive dwells ('on empty abdomen'). First, isochrone maps (VAT maps) from both study groups (patients on PD and controls), were plotted. Then, based on the group-mean VAT maps obtained for the control

children and PD patients, a specific map of distribution of statistically significant VAT value differences was created in order to analyze possible ventricular conduction disorders in ESRF patients on PD.

In order to create a 'differences map', the mean VAT values for each electrode site were calculated for both groups, taking into account a confidence interval at significance level of $\alpha = 0.05$. If calculated values contained within this interval corresponded to the 0 value on the map, it meant no difference. Positive values indicate an earlier, while negative ones a later arrival of the activation front to the given ventricle site as compared to the corresponding site on the group-mean VAT map for the control group. Calculated VAT differences, resulting from multiple comparisons of the VAT maps for the studied groups, were presented as the isochrone map of VAT value differences. For calculations of VAT differences between the group-mean VAT maps from the control and PD groups, Excel 2010 (Microsoft Corporation, Irvine, CA, USA) software was applied.

All the parents of the examined children and adolescent minors enrolled in the study gave their informed consent to their children's participation in the procedure. The investigation protocol was approved by the local ethics committee and was compliant with the Declaration of Helsinki.

STATISTICAL ANALYSIS

The data are presented as arithmetic means with standard deviation ($\bar{x} \pm SD$). Their statistical significance of the null hypothesis for the equality of means, expected for particular studied characteristics in Group I and II, was verified by the Mann-Whitney's nonparametric test.

RESULTS

Table 1 presents selected demographic and clinical data of the ESRF patients treated with PD, while Table 2 depicts the biochemical characteristics of the patients.

Left ventricular hypertrophy was excluded in all PD patients, based on ECHO findings. Values of LVM and LVMI did not exceed the 95th percentile, as referred to the normative data reported by Khoury *et al.* (15). In all PD children, ECHO parameters of overall contractility, ejection fraction (EF) and shortening fraction (FS), showed normal left ventricle systolic function.

VAT MAPS IN THE CONTROL GROUP

While evaluating a distribution of isochrones on the group-mean VAT map obtained for the control children (group II), it was found that the activation process of

heart ventricles began at approximately 15 ms in the subendocardial layer of the left lower surface of the interventricular septum and in a part of the free left ventricle wall (Figure 1).

During further 20–30 ms, a depolarization wave passes from the left to the right side of the interventricular septum

to trigger the active state in the subendocardial free areas of the right and left ventricle walls. Simultaneously, the working muscle is activated starting from the branches of His bundle. Final depolarization phase is seen on isochrones maps during approximately 60 ms on the right side of the anterior thorax and in the upper part of the

TABLE 1
Demographic and Selected Clinical Data of the Groups in the Study

Index	Group	Age (year)	Sex M/F	Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)	Body mass index
I (PD patients)	n=10	13.6±2.31	4/6	122±3	68±4	18.68±2.32
II (controls)	n=26	14.3±1.6	12/14	118±3	66±5	21.02±1.37
P		NS		p<0.001	NS	p<0.001

PD = peritoneal dialysis.

TABLE 2
Biochemical Characteristics of Children in the Study

Index	Group	Urea (mg/dL)	cr (mg/dL)	t-Ca (mg/dL)	P _i (mg/dL)	Na (mmol/L)	iPTH (pg/ml)	Albumin (g/dL)
I (PD patients)	n=10	95.32±7.12	6.71±1.00	9.35±1.35	5.89±0.33	138.77±3.19	556.44±399.14	4.02±0.28
II (controls)	n=26	29.11±9.45	0.73±0.08	10.03±1.11	4.78±0.9	140.44±2.92	26.3±8.98	4.1±0.11
P		p<0.001	p<0.001	NS	p<0.001	NS	p<0.001	NS

cr = creatinine; t-Ca = total calcium; P_i = inorganic phosphate; Na = sodium; iPTH = intact parathormone; PD = peritoneal dialysis.

Figure 1 — VAT maps obtained for controls and PD children, and VAT value differences map. *Left panel:* Group-mean VAT map for the control group. *Middle panel:* Group-mean VAT map for the PD group. *Right panel:* Map of VAT values statistically significant differences created from the two group-mean VAT maps. Map *a* – on the plane; map *b* – 3-dimensional view.

shoulders, depicting the active electric state at the base of the heart ventricles and interventricular septum.

VAT MAPS IN CHILDREN ON PERITONEAL DIALYSIS

In the ESRF patients treated with peritoneal dialysis, a distribution of isochrones on the group-mean VAT map turned out to be partially different than in the control group. The observed abnormal pattern is compliant with early block of anterior fascicle of the left His bundle.

Similarly, as on VAT maps for the controls in PD patients, the subendocardial layer of the left lower surface of the interventricular septum is activated first. In the subsequent phase, the activation wave spreads from the left to the right side and then to the subendocardial areas of the free right ventricle wall. Since probably a blockade in the anterior fascicle of the left His bundle occurs, the left ventricle wall is finally activated but with some delay through the alternative pathway, i.e. by the posterior fascicle of the left His bundle.

In the final stage of ventricular depolarization, activation is directed towards the free wall of the left ventricle. The longest VAT values are found in the upper part of the shoulders and in the right anterior part of the thorax.

In the next step, a map presenting the statistically significant differences between the VAT values on the group-mean maps for the studied groups was constructed.

A map of VAT differences shows that in the entire lower anterior thorax, from the right axillary line up to the left axillary line, VAT values recorded for PD patients look no different from the VAT values obtained for the control group. However, VAT value differences between the groups occur exclusively within the upper right part and the left part of the anterior thorax and encompass almost the whole back. The darker areas, which correspond to the VAT differences, demonstrate a growing delay in the activation spread caused by the left His bundle blockade. A part of the delayed activation passes also onto the upper anterior part of the thorax. The higher differences at the region of the upper electrodes, up to the left shoulder-blade line, resulted from the expressly increased VAT values in the final ventricular depolarization.

A map of the significant VAT differences enables identification of the early block within anterior fascicle of the left His bundle in the peritoneally dialyzed children. This disturbance can be evident both from a distribution of isochrones and from numerical VAT values. It is worth noting that the ventricular conduction abnormality was not observed on the standard ECG recordings, because it appears beyond the thoracic area monitored by the routinely used 12-lead ECG.

DISCUSSION

Long-term observations showed that one third of patients on peritoneal dialysis demonstrated cardiovascular disease (CVD). According to Chavers *et al.*, cardiovascular disorders, often initially asymptomatic, include arrhythmia (19.6%), valvular disease (11.7%), cardiomyopathy (9.6%) and cardiac arrest (3%) (16).

There are numerous factors which are conducive to CVD development (16,17,18), including traditional risk factors (e.g. hypertension and dyslipidemia) and uraemia-related factors (toxaemia, overhydration, electrolyte disorders, anaemia, secondary hyperparathyroidism, hypoalbuminaemia, oxidative stress, chronic inflammation, malnutrition), and ineffective RR control (2,6,8,17).

Our study was planned to verify a hypothesis that children on PD have some subclinical disturbances in the ventricular conduction process that could be detected using an original technique of 'VAT differences map' of higher sensitivity than standard ECG.

The study revealed that a group-mean VAT map for the PD children, after normal intraventricular activation route in the initial stage (up to 20 ms), presents activation expansion, from the left to the right side in the subsequent phase and, further on, towards the subendocardial layer of the free right ventricle walls.

A map displaying the statistically significant differences between the VAT values obtained for the group-mean VAT maps in the two study groups: control children and ESRF children on PD, confirmed a presence of the delayed activation front that passes through the posterior fascicle of the left His bundle, avoiding the blockade in the anterior fascicle. Also, the last phase of ventricular depolarization had a slightly different course in controls, the anterior fascicle, and in dialyzed children, in whom, the highest differences of VAT values focused in the upper shoulders and in the right anterior thorax.

Pattern of abnormalities on the VAT differences map advocated for a diagnosis of a block of anterior fascicle of the left His bundle. It should be emphasized that on the standard ECG recordings from all ESRF children, no heart conduction disorders were found.

Contrary to Bosch *et al.* who, using 24-h ECG Holter monitoring in children with various stages of CKD, did not find any life-threatening ventricular arrhythmias (19), Scharer *et al.*, observed in 50% of the examined CKD children provisionally elongated time interval on electrocardiogram (QT), which may be a trigger for ventricular arrhythmia (20).

In our opinion, a delayed time of intraventricular activation could be detected in our PD patients because multielectrode BSPM recordings are able to catch the

abnormal ECG signals available far beyond the chest area monitored by the standard 12-lead ECG.

Some authors have stated that standard ECG in CKD patients is of lower diagnostic value as compared with the general population (21).

BSPM is documented to provide valuable electrophysiological data of ventricle activation areas and of ischemia localisation in the myocardium (22). Up to now, there are few reports on using isochrone (VAT) maps to monitor ventricular conduction abnormalities. Isochrone maps used to be applied for improving a clinical diagnosis of ventricle hypertrophy or various types of bundle branch blocks (23,24,25). Unfortunately, VAT maps are not used enough to recognize cardiac conditions in patients with CKD. The authors of this paper published some results in this field (10,26).

There are many possible alterations underlying the ventricular conduction disturbances observed in our study. Calcium-phosphate metabolism disorders are reported to be almost equally, responsible for the development of CVD in CKD patients, along with hypertension and dyslipidemia (17). In our PD children, significantly high levels of parathormone (PTH) were found. According to many authors, PTH is thought to be the main uremic toxin. High levels of iPTH cause mitochondrial lesions and energetic turmoil in cardiomyocytes (27,28,29). PTH also induces increased inflow of Ca ions to cellular cytoplasm, causing a disturbance in electric impulse transfer between cells. The pathomechanism described above could be responsible for ventricular activation delays on VAT maps from our PD children.

Bearing in mind the clinical severity of heart involvement in a course of ESRF, it seems obvious that every kind of new diagnostic tool is worth considering. BSPM is a non-invasive electrocardiographic method of higher sensitivity and specificity than standard ECG, which could be helpful in identification of covert changes in the heart conduction system in ESRF patients.

The main shortcomings of the present study were the limited number of patients treated with PD as well as a short time of observation. We intend to continue this pilot study, increasing the number of PD patients and the follow-up period.

CONCLUSION

1. VAT maps (isochrone maps) can be useful in detecting abnormal spreading and depolarization through the heart ventricles.
2. A map of VAT differences makes it possible to identify early disturbances of intraventricular conduction in the left branch of His bundle in ESRF children treated with PD who demonstrate normal 12-lead ECG.

3. Further studies on a larger group of children with ESRD treated by peritoneal dialysis are required to verify the reported preliminary observations.

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