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NMR-Relaxometer for Diagnosis and Control of Chronic Kidney Disease Patients Parameters (Urea and Creatinine)

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Abstract

Determination of disease stages and control of changes in blood and plasma during kidney injury (KJ) cure can be done using nuclear (proton) magnetic resonance (NMR) parameters dependences from physical-chemical parameters of blood changes. NMR spectroscopy allows the monitoring of molecular recognition processes in solution. For realization of this approach the low field NMR relaxometer was elaborated. Measurements of relaxation parameters were performed. Dependences of relaxation times T2A from urea and serum creatinine were received.

Keywords

Acute, Kidney, Injury, Nuclear, Magnetic, Resonance

Subject Areas: **Biochemistry, Biophysics**

Acute kidney injury (AKI) is one of the popular topics of discussions due to increasing development of spectroscopic methods recently. The disease progression and prognosis may be determined by this method in blood and urine specimens. Since AKI is associated with disease conditions, prevention and early detection of AKI becomes important in clinical settings. Early detection of AKI and its subsequent resolution using spectroscopy parameters could predict subsequent development of intrinsic AKI, dialysis requirement, duration of intensive care and finally affect mortality.

Chertow and colleques noticed that a rise in serum creatinine (SCr) of just ≥0.3 mg/dl had a four-fold higher multivariable-adjusted risk of death [1]. The AKI Network (AKIN) group modified the AKI definition based on RIFLE classification [2] classified the patients with the change in SCr ≥ 0.3 mg/dl (≥26.4 μmol/l) within 48

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hours as AKIN stage I, whereas patients receiving renal replacement therapy are included in AKIN stage 3.

Nuclear magnetic resonance (NMR), especially MR-tomography has become a familiar term in medical community. This is due to the advance and powerfulness of NMR-methods. But there exists some hesitations to examine by this method high risk patients (e.g. under sedation or anaestesia, stroke etc.), because powerful magnet fields affects the general state of patients.

Contemporary diagnosis is oriented on the non-invasive and nondestructive forms. Medical ordinary clinics need cheap devices for early identification and determination of disease stages and control of their cure stages and changes in blood physchemical parameters during kidney disease cure.

It can be done using nuclear (proton) magnetic resonance (NMR) parameters dependences from physical-chemical characteristics of blood changes. NMR spectroscopy allows the monitoring of molecular recognition processes in solution. Nowadays, a plethora of NMR methods are available to deduce the key features of the interactions in tissues and blood components [3]. To realize such approach the suitable device is to be elaborated and corresponding NMR relations between NMR-spectroscopic parameters and blood characteristics must be revealed.

We constructed and proposed portable low field NMR-relaxometer, presented at **Figure 1**.

Its power supply is autonomous—from accumulator or grid. Control and data processing is performed by Notebook. Portable magnetic system is constructed from NdFeB alloys with magnetic field B_0 = 0.242 Tl. Inhomogeneity of B_1 < 2% in 75% of its coil volume. Coefficient of sensitivity is $K = \nu_0^2 \cdot D^3$ [MHz^{2}cm^3] = 2700 - 4150, where proton resonance frequency ν_0 = 10 - 12 MHz, D = 10 - 30 mm—diameter of the probe head coil. Consumed power P < 15 VA. Mass < 15 kg. Error of NMR-parameters measurements ± 4% [4] [5].

Measurements of relaxation parameters were performed by Carr-Purcell-Meiboom-Gill-method [6] using 90°-τ-$(180^\circ$-2τ-$)_N$ pulse sequence, where N-number of 180°-pulses. Two spin-spin relaxation times T_{2A}, T_{2B} with corresponding proton populations P_{2A}, P_{2B} corresponding to water and albumin were observed. For T_{2A} we used measurement parameters: period of sequences T = 6 s, interval between pulses τ = 200 - 400 μs, number of pulses N = 5000, number of accumulations n = 3. For T_{2B}: T = 200 ms, τ = 200 μs, N = 100, n = 50 - 100 in the regime of water phase saturation.

Previously at resonance frequency ν_0 = 100 MHz using NMR spectrometer Tesla-BS 100 we obtained NMR-spectra of blood plasma in the frequency range ν = 99 - 100 MHz, presented at **Figure 2**.

In the range of chemical shifts $\delta_1 = \nu_1/\nu_0 \approx -1$ - 2.5 ppm (in the right side of spectra) was observed a series of peaks with common intensity 38.5% (integral intensity of the whole spectra is 100%), corresponding to -CHO, -CH_2 and -CH_3 groups of albumen molecules. At $\delta_2 = \nu_2/\nu_0 \approx 4$ - 6 ppm appear series of highly resolved peaks (with common intensity 47.2%), corresponding to water molecules at different states in blood plasma. Line widths $\Delta\delta$ of albumen peaks are $\Delta\delta \approx 2$ - 5 Hz. For water peak sit is $\Delta\delta \approx 1$ Hz. Calculations of corresponding spin-spin relaxation times from the line widths were made using equation:

$$\left(T_2\right)_{\text{obs}}^{-1} = \left(T_2^*\right)^{-1} + \pi\Delta\delta \tag{1}$$

Figure 1. Portable low field NMR-relaxometer.

where T_{2obs}—observed relaxation time, T_2^*—relaxation time, caused by magnetic field in homogeneity. Considering that for water $\Delta\delta \approx 1$ Hz and $\left(T_2^*\right)^{-1} \approx \pi\Delta\delta^* = 3.14\times10^{-6}$, from spectra at **Figure 2** we from Equation (1) obtain $T_2 \approx 300$ - 400 ms relaxation times of blood plasma. For albumen they are expected to be $T_{2B} \approx 30$ - 40 mc with protons population $P_{2B} \approx 14\%$.

Really, from relaxation measurements using Carr-Purcell-Meiboom-Gill-method [6] it was established, that in plasma relaxation times T_{2A} and T_{2B} (see **Table 1**), values are near to calculated from spectra.

First column designate No. of patient, year of birth, before or after hemodialysis (HD), the second and third columns—measured T_{2A} and T_{2B}, fourth column—$P_{2A,B}$, fifth and sixth columns—changes of relaxation times.

Values of *Urea* (mol. weight = 60 a.u.) and serum *Creatinine* (m.w. = 113 a.u.), one the important parameters of kidney decease were measured in standard biochemical laboratory of Kazan State Medical Academy using LAHEMA set and Popper method. Obtained NMR-parameters dependences of corrected T_{2A}/Alb for albumen weight are presented at **Figure 3** and **Figure 4**.

Reserved dependences can be approximated with 95% confidence interval by relations:

$$U = 38.1 - 0.016 \cdot T_{2A} / \mathrm{Alb} \tag{2}$$

$$C = 1.61 \exp\left(-T_{2A} / 1257 \cdot \mathrm{Alb}\right) \tag{3}$$

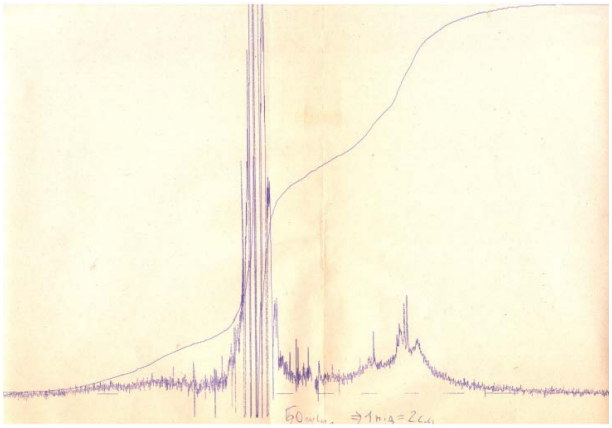

Figure 2. NMR-spectra of blood plasma.

Table 1. Relaxation times and there changes for different stages of chronic kidney decease.

No. patient/year of birth (y.b.)	T_{2A} (ms)	T_{2B} (ms)	P_A (%)	ΔT_{2A}/%	ΔT_{2B}/%
Patient of chronic kidney disease					
No. 1, 1950 y.b., before HD	667 ± 22	404 ± 70	95 ± 3	-	-
No. 1, after HD	519 ± 16	256 ± 42	94 ± 2	−148/−28.5	−148/−57.8
No. 1, after 1.5 years, before HD	529 ± 23				
No. 1, after 1.5 years, after HD	410 ± 4			−119/−29	
No. 2, 1941 y.b., before HD	671 ± 2	374 ± 25	97 ± 1	-	-
No. 2, after HD	577 ± 3	338 ± 70	97 ± 3	−94/−16.3	−6/−10.6
No. 3, 1942 y.b., before HD	468 ± 19	230 ± 26	89 ± 9	-	-
No. 3, after HD	377 ± 9	182 ± 30	89 ± 6	−91/−24.1	−48/−26.4
Healthy patients					
No. 1, 1980 y.b.	594 ± 14	284 ± 22	85 ± 3	-	-
No. 1, 1981 y.b.	575 ± 11	293 ± 20	88 ± 4	-	-

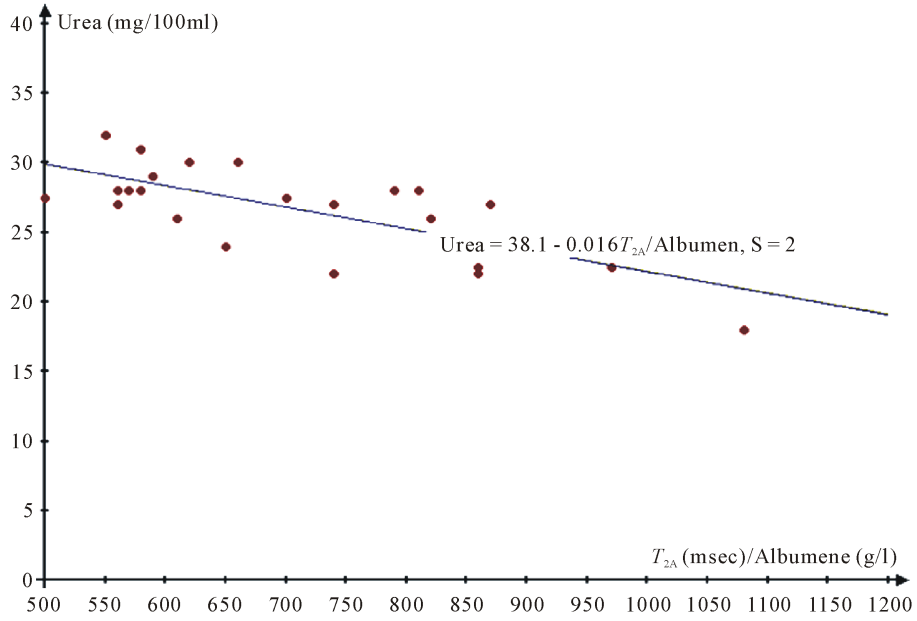

Figure 3. Dependence of Urea from T_{2A}/Alb.

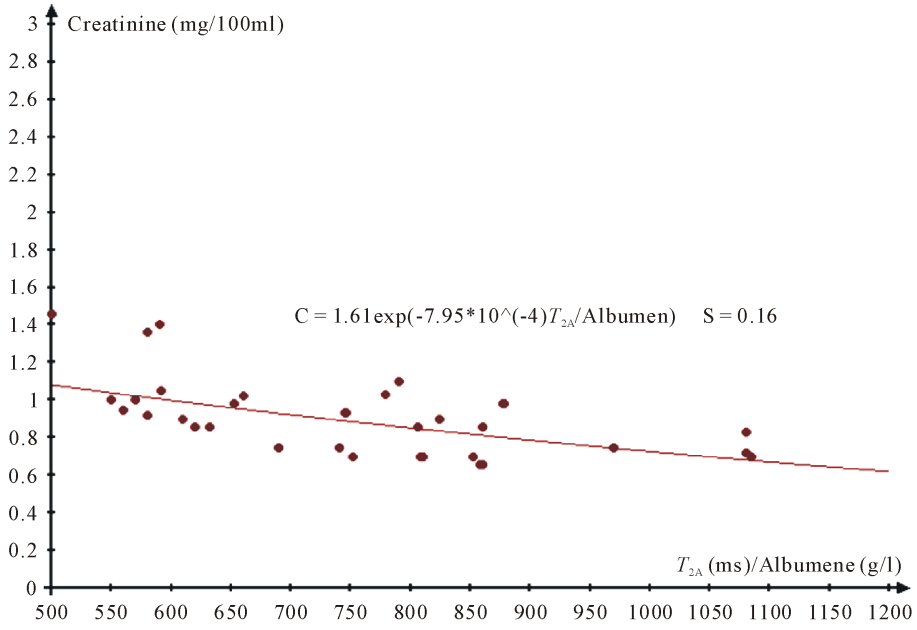

Figure 4. Creatinine from T_{2A}/Alb.

Standard deviation for urea and creatinine are 2.2 and 0.16 (±7.3% and ±14.6%).

Obtained results can be explained on the base of increase of substances with middle molecular weight (acting as endotoxines) at pathology, leading to decrease of T_{2A}.

At **Figure 5** presented dependence of T_{2A} from age t (years) of healthy men, which with the error 20 MS (~10%) can be approximated by linear equation:

$$T_{2A} = 0.8t + 141 \quad (4)$$

So, age must be considered at Urea and Creatinine determination. It should be also mentioned, that respiratory diseases (tonsillitis, grippe and headache) increase relaxation times on 15% - 30% from their average values, for

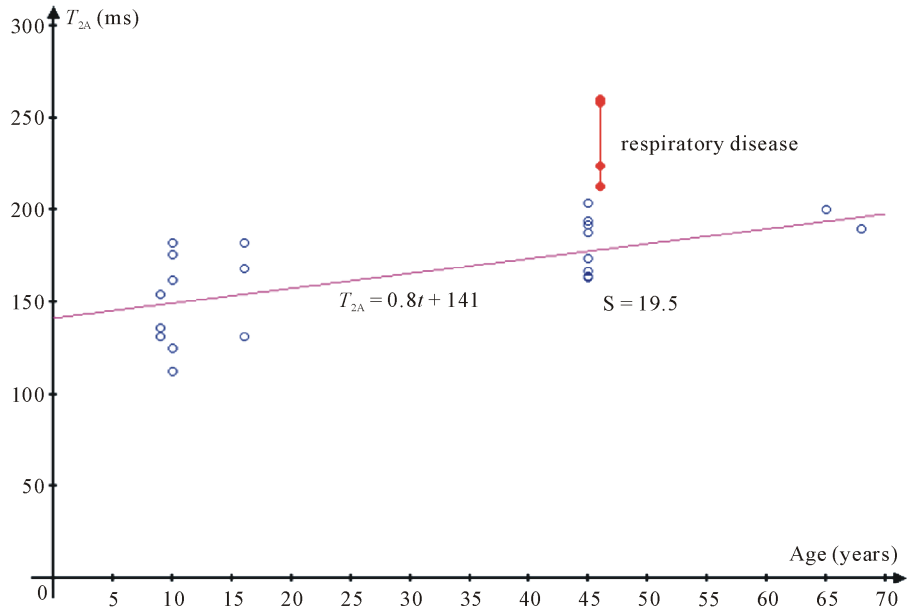

Figure 5. Dependence of T_{2A} from age of healthy men.

instance from T_{2A} = 180 MS to T_{2A} = 213 - 260 MS of 45 years old patient. At recover T_{2A} return to its individual norm.

Received results show, that NMR-relaxation method can be used for express-analysis of chronic kidney disease parameters before and after hemodialysis and characterizing different stages of AKI.

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