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Contrast Enhanced Ultrasonography in Diagnosis of Hypertensive Nephrosclerosis

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Abstract

Introduction: The hypertensive nephrosclerosis is difficult to diagnose especially in early stages due to the lack of methods, except the renal biopsy, considered the gold standard, which is rarely indicated in clinical routine due to its invasiveness. Therefore, a non-invasive method that can accurately assess the early changes of renal microvasculature could be a useful tool in early hypertensive nephrosclerosis diagnosis. **Objectives:** to evaluate if contrast enhanced ultrasonography (CEUS) has a diagnostic value in early diagnosis of hypertensive nephrosclerosis. **Methodology:** we studied 100 patients with essential arterial hypertension (HT) in different stages of the disease, diagnosed and treated according to the current guidelines and 20 healthy adult volunteers for comparison. After a complete clinical examination and specific laboratory tests, all subjects were investigated by CEUS with sulphur hexafluoride (SonoVue®, Bracco, Italy), administered in bolus in a cubital vein using a cannula of 20 Gauge, in a dosage of 1.2 ml, followed by 10 ml of saline solutions. The images with the displayed renal cortex were continuously recorded for 3 minutes, starting from the moment of injection. Then, all images were analysed using Contrast Dynamics Software from Siemens S2000 equipment (Siemens, Germany). **Results:** Both qualitative - real-time observation of the renal vascular phases - and quantitative evaluation – time intensity curves (TIC) analyse - showed significant differences in the enhancement parameters. AT (arriving time), PI (peak intensity) and AUC (aria under the curve) are the most well correlated parameters with the grade of the hypertension. No adverse effect was noted during and after CEUS examinations. **Conclusions:** CEUS accurately assess the renal microvasculature damage and may be a method that contributes to the early diagnosis of hypertensive nephrosclerosis in daily clinical practice.

Keywords: arterial hypertension, contrast-enhanced ultrasound, hypertensive nephrosclerosis

Rezumat

Introducere: Nefroangioscleroza hipertensivă este dificil de diagnosticat în special în stadiile precoce ale bolii din cauza lipsei metodelor de diagnostic, exceptând biopsia renală, considerată "gold standard", rareori indicată în practica clinică curentă datorită invazivității acesteia. De aceea, o metodă non-invazivă care poate evalua cu acuratețe modificările precoce ale microvascularizației renale, poate fi o metodă utilă în diagnosticul precoce al nefroangiosclerozei hipertensive. **Obiective:** de a evalua dacă ecografia cu substanță de contrast (CEUS) are o valoare diagnostică în depistarea precoce a nefroangiosclerozei hipertensive. **Metodologie:** am studiat 100 de pacienți cu

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hipertensiune arterială esențială (HT) de diferite grade, diagnosticați și tratați conform ghidurilor în vigoare și 20 de adulti voluntari sănătoși pentru comparare. După examinarea clinică și paraclinică specifică completă, toți subiecții au fost investigați ecografic cu hexaflourură de sulf (SonoVue®, Bracco, Italia), administrată intravenos in bolus în vena cubitală pe o branulă de 20 Gauge, în doză de 1,2 ml, urmată de 10 ml de ser fiziologic. Imaginile încărcării cu contrast ale parenchimului renal au fost înregistrate continuu timp de 3 minute începând din momentul injectării. Ulterior, au fost analizate cu softul de cuantificare - Dynamic Contrast - al ecografului S2000 (Siemens, Germania). **Rezultate:** Atât evaluarea calitativă – observarea în timp real a fazelor vasculare renale, cât și evaluarea cantitativă – analiza curbelor de încărcare în timp (TIC), au arătat diferențe semnificative la nivelul parametrilor de încărcare cu contrast. AT (timpul de ajungere al substanței de contrast în parenchimul renal), PI (intensitatea maximă) si AUC (aria de sub curbă) sunt parametrii corelați cel mai bine cu gradul hipertensiunii. Nici un efect advers nu s-a înregistrat în timpul și după efectuarea CEUS. **Concluzii:** CEUS evaluează cu acuratețe afectarea microvasculară renală și poate fi o metodă care contribuie la diagnosticul precoce al nefroangiosclerozei hipertensive, în practica medicală curentă.

Cuvinte cheie: hipertensiune arterială, ecografie cu substanță de contrast, nefroangioscleroza hipertensivă

INTRODUCTION

The link between kidney damage and HT remains a challenge in medical research from a century when HT concept was defined, taking in consideration than HT is a major risk factor for cardiovascular disease mortality worldwide, due to the increasing prevalence, poor compliance to treatment and many complications[1-3]. The hypertensive nephrosclerosis is currently diagnosed in the latest stages of the disease because, for a long period of time, the injuries are compensated by kidney and therefore the clinical presentation is not specific[4]. The current diagnostic methods are non-specific, especially for early diagnosis of hypertensive nephrosclerosis, except the renal biopsy which is considered the gold standard but is rarely indicated in clinical routine due to its invasiveness and possible severe complications[5]. The pathogenic mechanism is complex and not very well understood but renal microcirculation impairment seems to be responsible for the onset and progression of this disease[6]. Therefore, any method that can accurately assess the early microvasculature changes of renal cortex, easy to use, simple and safe, with no invasiveness, could be an important diagnostic tool in hypertensive nephrosclerosis approach.

CEUS is a promising new imaging technique that meets all these requirements and who can properly evaluate the early microvasculature damage in renal cortex, without any effect on renal function[7-9].

OBJECTIVES

The aim of this study was to evaluate the role and the value of CEUS in early diagnosis of hypertensive nephrosclerosis.

METHODS

This is a prospective and observational study, implemented in Cardiology and Internal Medicine Clinic of "Th. Burghele" Clinical Hospital in Bucharest, with the goal of enrolling over 100 patients with essential arterial hypertension (HT) in different stages of the disease and healthy adult volunteers (20 subjects) for comparison.

The inclusion criteria were the essential arterial hypertension (HT), diagnosed according to 2013 ESH/ESC Guidelines (systolic blood pressure >140 mm Hg and / or diastolic blood pressure >90 mmHg), with or without associated co-morbidities, treated or not with antihypertensive medications, age: 25-75 years old, both sexes. Were excluded patients with secondary hypertension, advanced atherosclerosis, diabetes mellitus, heart failure (with ejection fraction <50%), dehydrated patients, age under 25 and over 75 years old, severe liver diseases, neoplasia and patients with contraindications to SonoVue® administration (shunts right-left, severe pulmonary hypertension – pulmonary artery pressure >90 mmHg, uncontrolled hypertension, acute respiratory distress syndrome, in association with dobutamine in patients whose clinical condition suggests cardiovascular instability and dobutamine is contraindicated, pregnant and breastfeeding women, known hypersensitivity to sulphur hexafluoride or any of the SonoVue® excipients).

The consent form was signed by all subjects prior to enrolment.

A complete clinical examination and laboratory specific tests were done for all subjects. Then, glomerular filtration rate (eGFR) was calculated using Cockcroft-Gault formula. Before CEUS examinations the blood

pressure was taken for all enrolled subjects, after 15 minutes of sitting position. Systolic blood pressure for all subjects was between 100 and 140 mmHg and diastolic blood pressure was between 60 and 86 mmHg. An abdominal ultrasound examination was performed for each subject with storage of the relevant morphological and Doppler data images. Then, the right kidney was chosen for CEUS examination. All the necessary adjustments were made for the best visualisation of the renal parenchyma. The subjects were advice to breath slowly for a proper display of the right kidney coronal section plan. Then 1.2 ml of sulphur hexafluoride (SonoVue®, Bracco, Italy) was intravenously administered in bolus in the left cubital vein using a 20 Gauge cannula followed by 10 ml of saline solution. Starting from the moment of contrast injection, all images were continuously registered for 3 minute.

SonoVue® is a second generation ultrasound contrast agent, strictly intravascular, containing an inert gas (sulphur hexafluoride) which is totally eliminated from the body in 15 minute after injection by expiration (without any effect on renal function) and phospholipids, which are mixed with 5 ml of saline solution for the microbubbles reconstitution. The medium diameter of the obtained mirobubbles is between 2.5-6 μm[10,11]. In few seconds after the contrast intravenous administration, the microbubbles get into the arterial circulation and the renal cortex is displayed.

The ultrasound equipment used in this study is Acuson S2000 (Siemens, Germany), probe 2.5-5 MHz, with Cadence Pulse Sequences and Dynamic Contrast Enhanced software version 3.0 included, for time-intensity curves (TIC) analysis.

CEUS images analysis was performed in a qualitative and quantitative manner. The qualitative evaluation (real time observation of the renal vascular phases) assesses the enhancement of the renal cortex in: early cortical phase when intra-renal segmental arteries are filled with contrast (normally in takes between 11-14 seconds from the moment of injection), late cortical phase when renal cortex has an intense and uniform contrast enhancement (normally it takes between 20-40 seconds form the moment of injection) and medullar phase when the intensity of contrast in renal medulla progressively increase (normally it takes between 45-120 seconds from the moment of injection). For the quantitative evaluation (TIC analyse) the region of interest (ROI) was chosen with cortex and medulla included. Then, the enhancement TIC parameters were calculated for ROI: AT (arriving time), TP (time to peak), PI (peak intensity), AUC (area under the curve) and MTT (mean transit time). They were compared between grades of the HT and control group.

Statistical analysis

The statistical analysis was made with SPSS 20 software version. Student *t* test and Mann-Whitney non-parametric test were used for comparison between HT group's data and control. Variance analysis was used for this. The study dates were expressed as mean ±SD. P-value <0.05 was considered statistically significant.

RESULTS AND DISCUSSION

100 HT patients were included in this study (45 males and 55 females, age = 60.98 ±10.95) in different stages of the disease: grade 1 = 15 patients, grade 2 = 35 patients and grade 3 = 50 patients and 20 healthy adults volunteers for comparison (8 males and 12 females, age = 50.82±11.08).

The study group was homogenous as age in order to exclude the physiological differences in renal function even, the most numerous and elderly patients were included in grade 3 HT. From basic clinical data of the patients we've noted that the estimated glomerular filtration rate (eGFR) and blood urea nitrogen (BUN) are best well correlated with the grade of HT ($p<0.01$). Also, the serum creatinine is significantly increased ($p<0.01$) in the latest stages of HT. Blood glucose (Glu), total cholesterol (Tch) and LDL cholesterol were significantly higher in all stages of HT as compared with control group ($p<0.01$). Body mass index (BMI) was increased in HT group vs. control ($p<0.01$). Proteinuria was observed at grade 2 HT and significantly increases (more than 100%) in grade 3 HT. Red blood cell (RBC) decreases in grade 3 HT vs. healthy and HT grade 1 ($p<0.01$). No variations observed among the group related to haemoglobin (Hb), haematocrit (Ht), uric acid (UA) and urinary density (Table 1).

The real time observation of the renal vascular CEUS phases shows differences in vascular dynamic patterns of contrast distribution in renal cortex. A shorter cortical phase in latest grades of HT (with a significant delay of start of the early cortical phase), a decrease of the intensity contrast enhancement in renal cortex and a shorter medullar phase in HT groups versus control (Figure 1).

Similar results as real time observation of the renal cortex enhancement shows the qualitative evaluation of the renal microvasculature. The early cortical phase started at 19.20±8.78 seconds from the contrast injection time in total HT group as compared to 11.22±1.43 seconds in the control group ($p<0.01$). There is a pro-

Table 1. Basic clinical data of the study group**

	HT Grade 1	HT Grade 2	HT Grade 3	HT Total	Control
N	15	35	50	**100**	20
Sex					
Male	8	17	20	**45**	8
Female	7	18	30	**55**	12
Age (years)	52.20±13.74	61.00±8.98	65.05±9.77	60.98±10.95	50.82±11.08
BMI (kg/mp)^{a*,b,c,f*}	28.80±3.77	28.28±5.62	28.59±5.18	28.51±5.09	25.60±3.01
Hb (g/dl)	14.50±1.49	14.11±1.82	13.58±1.42	13.87±1.56	14.15±1.02
Ht (%)	42.66±4.29	41.75±4.99	40.47±4.10	41.11±4.38	40.52±3.12
RBC (106 µl) ^{c*,d,f}	4.92±0.53	4.72±0.61	4.51±0.46	4.55±0.51	4.91±0.57
Glu (mg/dl)^{a*,b*,c*,f*}	105.08±10.06	124.07±53.92	111.59±26.78	114.71±36.92	90.65±10.12
TCh (mg/dl)^{a*,b*,c*,f*}	217.42±32.61	213.63±50.33	212.07±48.71	213.29±47.01	185.41±24.43
LDL (mg/dl)^{b*,c*,f*}	131.08±49.83	141.29±52.26	135.01±44.92	136.48±47.69	101.29±44.91
UA (mg/dl)	6.14±1.25	5.73±1.40	6.15±1.85	6.01±1.66	6.32±7.51
BUN (mg/dl)^{b,c*,d*,e*,f*}	36.88±7.45	38.20±11.61	52.74±27.09	45.81±22.28	31.22±9.10
SCr (mg/dl)^{c*,d*,e,f}	0.89±0.16	0.91±0.29	1.11±0.61	1.01±0.50	0.80±0.05
GFR (mp)^{b*,c*,d*,e*,f*}	89.33±18.76	80.71±17.14	66.40±24.50	74.19±23.20	95.20±12.80
USG	1020.07±7.89	1018.54±7.29	1015.60±8.06	1017.15±7.90	1016.17±5.62
Urine Proteins					
Yes	0	5	13	18	0
No	15	30	37	82	20

**Data = mean ± SD
a) p <0.05, HT Grade 1 versus Control; b) p <0.05, HT Grade 2 versus Control; c) p <0.05, HT Grade 3 versus Control; d) p <0.05, HT Grade 3 versus HT Grade 1 ; e) p <0.05, HT Grade 3 versus HT Grade 2; f) p < 0.05, HT Total versus Control
* = p <0.01

gressive delayed of the early cortical phase from grade 1 to grade 3 HT: 17.67±3.98 seconds in grade 1 to 20.70±11.17 seconds in grade 3 HT. The late cortical phase was also progressively delayed from 22.33±4.59 seconds in grade 1 to 24.96±11.48 seconds in grade 3 versus 15.46±1.54 seconds in control group. Also, the end of the medullar phase starts earlier in HT group (107.49±19.94 seconds) versus control (119.01±5.37 seconds) (p<0.01) (Table 2).

TIC analysis reveal significant differences of the enhancement parameters, well correlated with the progression of the disease in HT. Arriving time (AT) and peak intensity (PI) showed the highest sensitivity with the disease progression (p<0.01). As they accurately assess the renal microvasculature impairment in all grades of HT, we can consider them as valuable parameters in early diagnosis of hypertensive nephrosclerosis. Aria under the curve (AUC) showed significant differences between total HT group and control (p<0.01) but not very well correlated with the grade of the HT. Time to peak (TP) and mean transit time (MTT) are not well correlated with the HT grades (Table 3).

The impairment of the renal microvasculature is still a challenge in medical research field due to lack of the current diagnostic methods in delivering accurate structural and functional information.

CEUS is a new imaging technique that can accurately assess the renal microvasculature changes, using both qualitative (real time observation) and quantitative analyses (TIC analyse)[12,13].

In the present study we have shown that CEUS is a useful tool in renal microvasculature changes evaluation in HT stages, being a valuable method in early diagnosis of hypertensive nephrosclerosis. To the best of our knowledge, no previous studies have been done until now in HT using CEUS. A total number of 120 CEUS investigations were performed in this study with an average CEUS examination time of less than 15 minutes. No adverse effect or changes in biological and hemodynamic profile of the subjects were noted during and after CEUS examinations.

The renal HT induced changes increase the hemodynamic impedance of renal microcirculation, reduce the renal perfusion and lead to ischemia. In total HT group the display of the renal cortex was slower as compared to the control group. AT was longer and PI and AUC decreased progressively from grade 1 to grade 3 of HT. They can be considered as indicators for the disease progression, being valuable parameters in early diagnosis of hypertensive nephrosclerosis, suggesting that CEUS is a useful diagnostic method for the renal microvasculature changes assessment. Similar results

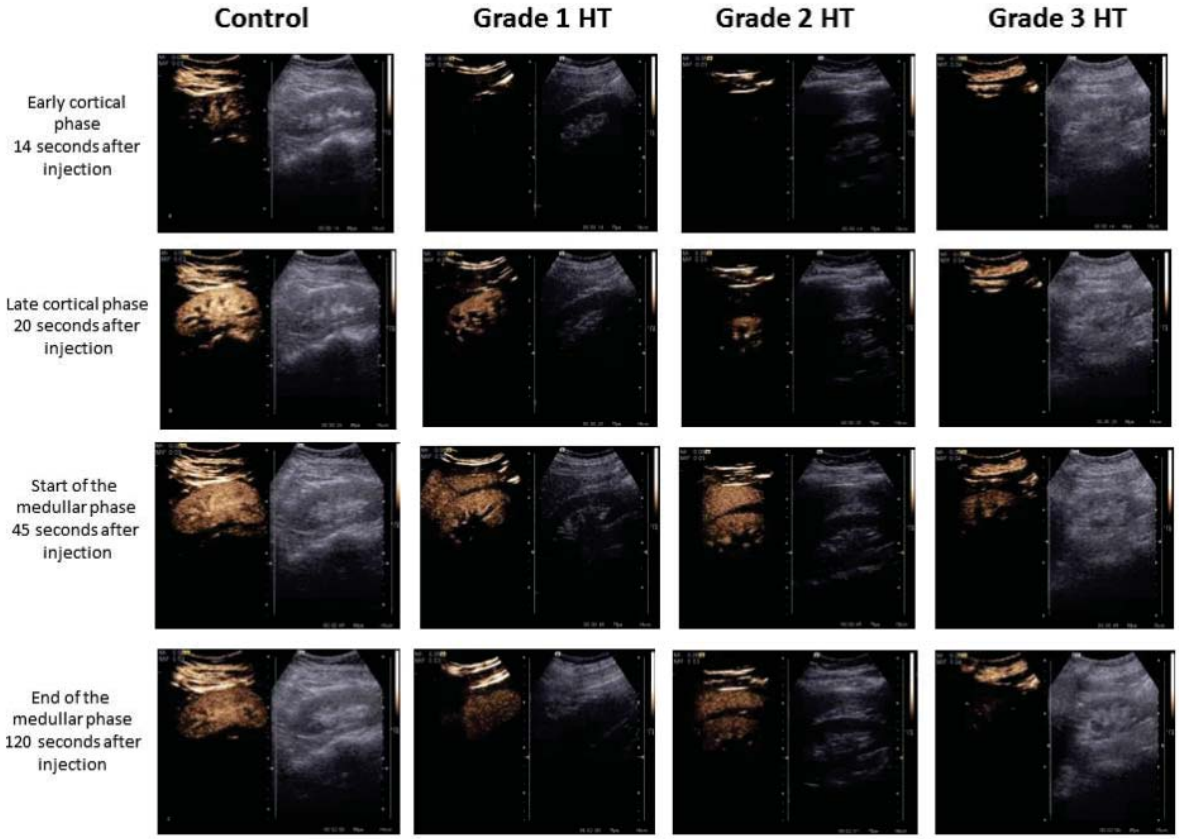

Figure 1. Real time observation of CEUS vascular phases in renal cortex.

were obtained by Fang Ma at al. in diabetic patients[14], Schneider et al. in cardiac surgery[15,16] and ICU patients[17] and Benozzi[18] and Kay[19] in transplanted kidney.

In early diagnosis of hypertensive nephrosclerosis, since other methods are not widely accepted, CEUS may be a useful diagnostic tool, easy to use, simple, safe and sensitive technique, reliable, without any exposure to radiation and no effect on kidney function, applicable even on critically ill patients with renal damage or to the bedside.

There are few limitations of the study. From actual data, it seems that the method cannot differentiate

Table 2. CEUS vascular phases of renal cortex: qualitative evaluation

Enhancement Phases		HT Grade 1 n = 15	HT Grade 2 n = 35	HT Grade 3 n = 50	HT Total n = 100	Control n = 20
Early cortical Phase (N:10-14 s)	Start[a*,b*,c*,d*]	17.67±3.98	17.43±4.47	20.70±11.17	19.20±8.78	11.22±1.43
	End[a*,b*,c*,d*]	21.00±4.75	20.46±5.19	23.81±11.29	22.31±9.03	14.50±1.41
Late cortical phase (N:20-40 s)	Start[a*,b*,c*,d*]	22.33±4.59	21.40±5.57	24.96±11.48	23.42±9.25	15.46±1.54
	End	41.20±4.00	40.37±5.28	43.03±14.20	41.90±10.91	39.55±1.27
Medullar Phase (N:45-120 s)	Start	43.53±3.93	43.06±5.06	45.50±13.78	44.39±10.61	42.34±1.90
	End[b*,c*,d*]	112.60±16.60	105.20±19.17	107.57±21.23	107.49±19.94	119.01±5.37

a) $p < 0.05$, Control versus HT Grade 1; b) $p < 0.05$, Control versus HT Grade 2; c) $p < 0.05$, Control versus HT Grade 3; d) $p < 0.05$, Control versus HT Total
*= $p < 0.01$

Table 3. CEUS quantitative evaluation: TIC analyse

	HT Grade 1	HT Grade 2	HT Grade 3	HT Total	Control
N	15	35	50	100	20
AT (s)[a*,b*,c*,f*]	16.47±4.22	16.31±4.19	19.95±11.21	18.29±8.86	9.94±1.55
TP (s)	42.57±7.48	43.02±17.20	46.50±17.84	44.81±16.55	45.01±6.37
PI (%)[a*,b*,c*,d*,e*,f*]	23.41±7.39	20.11±7.40	16.82±4.87	18.80±6.53	30.16±6.11
AUC (%s)[a,b*,c*,f*]	1660.96±838.17	1509.52±872.51	1470.14±738.20	1509.39±792.49	2423.01±1034.30
MTT (s)	61.62±13.30	63.54±23.79	66.74±23.95	65.00±22.61	68.47±12.55

a) p <0.05, Control versus HT Grade 1; b) p <0.05, Control versus HT Grade 2; c) p <0.05, Control versus HT Grade 3; d) p <0.05, HT Grade 1 versus HT Grade 3; e) p <0.05, HT Grade 2 versus HT Grade 3; f) p <0.05, Control versus HT Total
*= p <0.01

between hypertensive nephrosclerosis and other renal microvasculature damages (ischemic nephropathy, microvasculature impairment in diabetes) and also in patients with high risk of acute renal failure (dehydration, post-surgery, etc.). Studies with large cohort of patients of different pathologies as primary renal diseases (glomerular, tubular, etc.), diabetes mellitus, ischemic nephropathy, hypertension, etc. will still be needed to explore the relationship between the sensitive parameters and kidney pathological changes in order to establish the specificity of the method.

CONCLUSIONS

This study shows that CEUS accurately assess the renal cortical perfusion damage in HT using qualitative and quantitative analyses, being an important tool for early diagnosis and evolution of hypertensive nephrosclerosis. AT, PI and AUC are the most sensitive parameters in assessing the renal microvasculature impairment in different stages of the disease. CEUS with SonoVue® is a non-invasive, well-tolerated and safe method to accurately assess the renal microvasculature impairment in HT patients. Further studies are required to establish the feasibility of this new imaging technique in diagnostic management of hypertensive nephrosclerosis.

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