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Application of parametric ultrasound contrast agent perfusion studies for differentiation of hyperplastic adrenal nodules from adenomas—Initial study

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ABSTRACT

Objectives: To evaluate the possibilities of differentiation of non-malignant adrenal masses with the application of the new technique for the evaluation of enhancement after administration of an ultrasound contrast agent: parametric imaging.
Patients and Methods: 34 non-malignant adrenal masses in 29 patients were evaluated in a dynamic examination after the administration of ultrasound contrast agent with parametric imaging. Patterns on parametric imaging of arrival time were evaluated. The final diagnosis was based on CT, MRI, biochemical studies, follow up and/or histopathology examination.
Results: The study included: 12 adenomas, 10 hyperplastic nodules, 7 myelolipomas, 3 pheochromocytomas, hemangioma with hemorrhage and cyst. The pattern of peripheral laminar inflow of Sonovue on parametric images of arrival time of was 100% sensitive for hyperplastic nodules and 83% specific in regard to adenomas.
Conclusions: Parametric contrast enhanced ultrasound may accurately differentiate hyperplastic adrenal nodules from adenomas and could be complementary to CT or MRI. Incorporation of perfusion studies to CT or MRI could possibly enable one-shop complete characterization of adrenal masses. This could deliver additional information in diagnostics of patients with Conn Syndrome and warrants further studies in this cohort of patients.

1. Introduction

Ultrasound as a high resolution, real time non-invasive, cheap and easily accessible modality is frequently used for the evaluation of patients with neoplastic diseases, arterial hypertension and endocrine dysfunction in whom the adrenal lesion may be expected. Abdominal ultrasound can also incidentally detect adrenal masses termed as incidentalomas. Ultrasound may be applied for follow up of quite a large group of patients with adrenal incidentalomas who are not referred for surgery. Moreover endoscopic ultrasound is a prime method for evaluation of left adrenal gland masses. Ultrasound may visualize normal adrenal glands and more importantly enlarged adrenal glands (wings of glands >2–5 cm long and 6–10 mm thick) are detectable in a high percentage of cases [1–4].

Only some non-malignant adrenal masses present pathognomonic features on computed tomography, the examination of choice of adrenal glands [5]. However, proper diagnosis in this cohort of lesions is important for further management in certain scenarios.

Recently some new ultrasound modalities have been investigated in regard to adrenal masses differentiation (malignant vs. benign) [6–9] or within benign group of adrenal masses [10].

The aim of the study was to evaluate possibilities of differentiation of non-malignant adrenal masses with the new technique for evaluation of enhancement after administration of an ultrasound contrast agent – parametric imaging – as we hypothesized that the architecture of arterial vascularization of adrenal masses could be a differential factor.

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2. Material and methods

The approval for this study was obtained from the Ethics Committee of the Medical University of Warsaw, and all the patients provided an informed consent. 34 non-malignant adrenal masses in 29 patients were evaluated in a dynamic examination, after administration of bolus of 2.4 ml of ultrasound contrast agent Sonovue (Bracco) followed by a bolus injection of 2.5 ml of saline, with ultrasound scanner Aplio XG (Toshiba, Japan) and convex probe1–6 MHz, with low MI (MI = 0.06–0.09) contrast harmonic imaging sequence (CHI) in dual mode (CHI and B-mode simultaneously), with acquisition of a set of loops up to 3 min after contrast administration.

Patterns of parametric imaging (software by Toshiba, Japan) of arrival time and time-to-peak were evaluated [11]. Postprocessing - parametric imaging included: arrival time (AT) and time-to-peak (TP) images with different 3 time ranges: 7 s, 14 s, 21 s (of color scale that covered the respective time range). Zero point-time at the border of contrast arrival to the image. Settings: AT sensitivity at 40%, trigger at 10%; TP sensitivity at 10%, trigger 10%.

Arrival time patterns (their spatial distribution within the adrenal mass) were evaluated separately with parametric software and on the basis of video loops inspection and classified by consensus of two readers. Based on the onset of appearance of contrast agent in adrenal mass (characterizing the distribution of their arterial vascularization) we identified the following patterns of enhancement: peripheral, central, mixed-central and peripheral or lack of enhancement.

Times from the administration of Sonovue to its arrival to adrenal mass and neighboring reference organ as kidney or liver or spleen were also measured and evaluated.

The mean diameter of the adrenal mass was calculated from its 3 orthogonal diameters on B-mode axial and coronal non-contrast ultrasound images, acquired before the dynamic contrast enhanced study.

The final diagnosis was based on CT, MRI, biochemical studies, at least one year of follow up and/or histopatology examination following surgery (in 11 adrenal masses).

The statistical analysis included Statistica 10 (StatSoft Inc., USA) with W Shapiro–Wilk, *t*-Student, *U* Mann–Whitney and ANOVA Kruskala–Wallisa tests. Statistical significance was set at $\alpha \leq 0.05$.

3. Results

In the group of 29 patients there were 34 non-malignant adrenal masses evaluated with parametric images after contrast agent administration. These masses included 12 adenomas, 10 hyperplastic nodules, 7 myelolipomas, 3 pheochromocytomas, haemangioma with a haemorrhage and a cyst.

The mean diameter of all adrenal masses was 38.5 mm, range [9.7–102 mm]. The mean diameter of nodular hyperplasia masses was 26.6 mm, range [9.7–58.5 mm] and the one of adenomas 35.5 mm, range [16.3–56 mm] and they did not differed statistically ($p = 0.075$).

The patterns of enhancement within the groups of adrenal gland masses on arrival time, evaluated with parametric images and with cine loops inspection, are presented in Table 1 and Figs. 1 and 2.

The pattern of peripheral (onset of contrast enhancement at periphery) laminar (with time gradient) inflow of Sonovue (with complete filling of the mass or only at the edge of it) on parametric imaging of arrival time was 100% sensitive for hyperplastic nodules [Fig. 1] and 83% specific in regard to adenomas [Fig. 2]. It was also highly specific – 79% in regard to the whole group of benign adrenal masses. This criterion based on cine loops inspection was only 70% sensitive and 42% specific in regard to adenomas or to all benign adrenal masses.

Table 1
Arrival time patterns of adrenal masses on parametric imaging and cine loop evaluation.

Adrenal masses	Arrival time pattern (parametric)	Arrival time pattern (cine loop evaluation)
Hyperplastic nodules (10)	Peripheral 10	Peripheral 7 Central 1 Mixed 2
Adenomas (12)	Peripheral 2 Central 3 Mixed 7	Peripheral 7 Central 2 Mixed 3
Myelolipomas (7)	Peripheral 2 Central 3 Mixed 2	Peripheral 4 Mixed 2 Lack of enhancement 1
Pheochromocytomas (3)	Peripheral 1 Mixed 2	Peripheral 2 Mixed 1
Hemangioma	Central	Peripheral
Cyst	Lack of enhancement	Lack of enhancement

Linear regression test indicated high values of correlation coefficient [$r = 0.87649$ ($p = 0.0000$)] of times to first contrast enhancement of adrenal mass and neighboring reference organ. Statistical analysis did not show the differences of times to first contrast enhancement between main groups of benign adrenal masses (hyperplastic nodules, adenomas, myelolipomas) ($p = 0.1298$).

4. Discussion

So far ultrasound contrast enhanced studies of adrenal masses showed inconsistently efficacy of the technique to differentiate between malignant and benign adrenal masses. The study by Dietrich et al. indicated ineptitude to distinguish malignant and benign lesions [6]. On the contrary Friedrich-Rust at al suggested that contrast-enhanced ultrasound may be a useful method in diagnostic work-up of adrenal mass with excellent sensitivity for the diagnosing of malignancy [7]. They established 4 patterns based on times to first contrast enhancement: I = early arterial contrast enhancement (<20 s), II = arterial contrast enhancement beginning in the arterial phase (21–40 s), III = late and little contrast enhancement in the late phase (>40 s), and IV = no recordable contrast enhancement at all. All malignant lesions in their study presented patterns I and II with sensitivity 100% and specificity 67%. In our study, which included only the benign adrenal masses, we investigated the specificity of such approach that was only 2.9%. Our study did not show the differences of times to first contrast enhancement between main groups of benign adrenal masses. As we discovered high correlation of times to first contrast enhancement of adrenal mass and neighboring reference organ we also presume, as Mostbeck, that contrast enhancement time is primarily dependent on general patients factors (particularly heart-circulatory system function) than tumor characteristics such as vessel density or “pathological vessels” [12].

However, differences in spatial dynamics of first contrast inflow indicate differences in the vessel architecture of the examined adrenal masses. The new parameter, so called pattern of peripheral laminar inflow of Sonovue on parametric imaging of arrival time, was 100% sensitive for hyperplastic nodules and 83% specific in regard to adenomas. This criterion, based on cine loops inspection was only 70% sensitive and 42% specific. There are some differences in perception of contrast enhancement on parametric color maps and cine loops inspection. Parametric images that employ quantification to produce maps of vessel architecture seem to be more