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Contrast enhanced ultrasound evaluation of the kidney

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Abstract

In most centers, the first intention method used for kidney evaluation is ultrasonography, both in B and Doppler modes. CEUS evaluation adds valuable information; therefore it should be part of routine examination. Unfortunately, this is not always possible, given the high costs of dedicated ultrasound machines. However, the final cost will be lower than if CT or MRI assessment is used, in addition, the patient is not exposed to ionizing radiation, and the diagnosis can be made in the same place and in a very short time interval. Also, because the ultrasound contrast agent is not excreted by the kidneys, CEUS can also be used in acute or chronic renal failure, as opposed to CT evaluation.

Given the rich vasculature of the kidney, ultrasound contrast agent administration improve the visualization of avascular areas (small cysts, abscesses, hematomas, ruptures and renal infarctions) and of areas with very few vessels (if microbubbles are seen in the septa of complex cystic lesions, there is a high suspicion of malignancy). Also, a sensitive differential diagnosis can be made between malignant or benign tumors and normal anatomical variant, or between acute pyelonephritis and small micro-abscesses. Kidney CEUS could be used in the diagnosis of renal vascular diseases, in which, it appears that the prospects are good, especially for renal transplantation, where often repetitive evaluation is required.

Studies are still needed to establish clear criteria for the differential diagnosis between malignant and benign renal focal lesions.

Key words: contrast enhanced ultrasound, kidney, differential diagnosis

Rezumat

În majoritatea centrelor, evaluarea de primă intenţie a rinichiului se face prin ecografie, în mod B şi Doppler. Evaluarea prin CEUS aduce date suplimentare valoroase, din acest motiv trebuie să facă parte integrantă din examinarea de rutină. Din păcate, acest lucru nu este posibil întotdeauna, ţinând cont de costurile mari ale unei aparaturi ecografice performante, care să permită evaluarea prin CEUS. Oricum, în final, costurile vor fi mai mici decât prin evaluarea CT sau RMN, în plus pacientul nu mai este expus la radiaţii ionizante, iar diagnosticul se poate obţine în acelaşi loc şi într-un timp foarte scurt. De asemenea, datorită faptului că substanţa de contrast ecografic nu se elimină pe cale renală, evaluarea prin CEUS poate fi folosită în insuficienţa renală acută sau cronică, spre deosebire de evaluarea prin CT.

Ţinând cont de bogata vascularizaţie a rinichiului, administrarea contrastului ecografic ameliorează vizualizarea atât a zonelor nevascularizate (chisturi mici, abcese, hematoame, rupturi, infarcte renale), cât şi a celor foarte slab vascularizate (evidenţierea microbulelor în peretele sau septele unei leziuni chistice ridicând suspiciunea de malignitate). De asemenea permite diagnosticul diferenţial între prezenţa unei formaţiuni tumorale maligne sau benigne şi o variantă anatomică normală, sau, într-o pielonefrită acută, se pot evidenţia uşor microabcese renale. Evaluarea CEUS a rinichiul este utilă şi în diagnosticul afecţiunilor vasculare renale, unde, se pare că perspectivele utilizării CEUS sunt bune, mai ales în cazul transplantului renal, unde evaluări repetitive sunt adeseori necesare.

De asemenea, încă mai sunt necesare studii care să stabilească criterii clare de diagnostic diferenţial între formaţiunilor solide renale maligne sau benigne, la fel ca şi în cazul ficatului.

Cuvinte cheie: ecografia cu substanţe de contrast, rinichi, diagnostic diferenţial

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The use of ultrasound contrast agents is a big step forward in the world of ultrasound, opening new horizons for the assessment of multiple abdominal organs. As it is well known, the utility of contrast enhanced ultrasound (CEUS) for focal liver lesions evaluation was fully demonstrated, being an accepted method of diagnosis. Re-

garding the kidney, the method has not yet been accepted as a standard way of assessment, being considered "off-label". To use or not CEUS to diagnose a patient with kidney pathology is a decision that must be taken after weighing the risk-benefit ratio, for each case, based on the available scientific data [1].

In most cases, ultrasonography is the standard method for the first intention evaluation of the kidney. It brings valuable information regarding the kidney size, revealing hydronephrosis and focal kidney damage, and by Doppler examination, renal vascular disorders can be diagnosed [2]. However, the differential diagnosis between simple renal cysts and mixed solid tumors is sometimes difficult only by standard ultrasound, and Doppler examination techniques usually do not ad significant information. In these circumstances it is expected that CEUS examination will bring valuable information [3].

1. Ultrasound contrast agents used for the evaluation of the kidney

Levovist® (Schering, Germany) was the first ultrasound contrast agent (UCA) available in Europe for the assessment of the kidney. The microbubbles contain air and the shell is made of galactose and palmitic acid, the latter as surfactant. It was originally used to amplify the Doppler signal and for the examination of the renal vascular bed, subsequently for the gray scale evaluation of the renal parenchyma [4]. Its current indications are cardiac ultrasound, transcranial ultrasound, abdominal ultrasound and the evaluation of vezico-ureteric reflux [1].

SonoVue® (Bracco, Italy) consists of microbubbles containing sulphide hexafluoride, embedded in a phospholipidic shell. Its current indications are cardiac ultrasound, the assessment of macro and micro-vascular abnormalities (brain vessels and peripheral arteries, portal vein) and the assessment of breast and liver tumors [1]. The evaluation of renal arteries with SonoVue is part of the classical indications, but the evaluation of renal parenchyma is not yet fully accepted, [4].

Optison® (Molecular Biosystems, USA, and Mallinckrodt, Germany) is composed of microbubbles of octafluor propane enveloped in albumin. The recommendations for its use are still limited to cardiac ultrasound, but there are promising data regarding the evaluation of the renal parenchyma [4].

2. Kidney behavior following UCA injection

Normally, the kidneys receive 20-25% of the cardiac output, 90% in the cortical area and 10% in the medulla. Unlike the liver, the kidneys do not have sinusoidal capillaries, so that the classical contrast enhancement phases seen in the liver are not present in the kidney. There are three key differences between kidney and liver behavior following contrast administration: first - absence of UCA accumulation in the kidney; second - no parallel portal type circulation (even if there is a very good communication between the capillaries originating in the Bowman capsule and those of the contort distal tubules); and third - a good visualization of the arterial and venous renal vascular tree [4].

Tumor tissue can be differentiated from the normal kidney according to enhancement behavior following UCA injection: tumoral neovascularisation enhances differently than the normal capillaries of the kidney [5]. UCA are strictly intravascular, so that they do not provide information regarding the kidney excretory function [1]. This is why they can be used in patients with acute or chronic renal failure and in patients with urinary obstruction, unlike contrast CT or MRI.

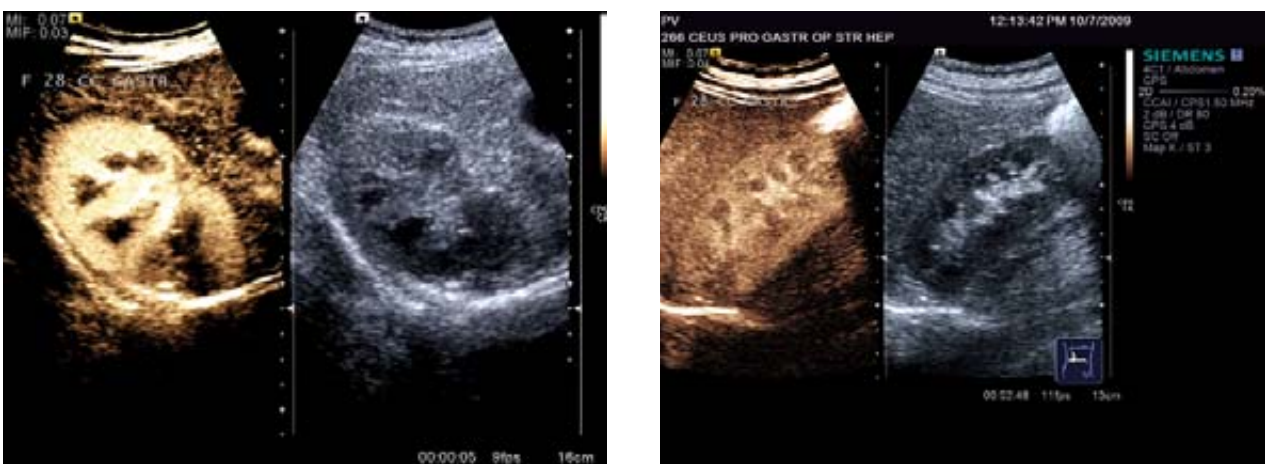


Fig 1. Normal kideney. **a.** Early enhancement of the cortical (9 s). **b.** Normal aspect in the late, parenchimatous phase.

3. The normal kidney on CEUS examination

Following contrast, artery filling occurs first, followed quickly by complete filling of the cortical area, 10-15 seconds after injection. The medulla enhances slower, so that in 30-40 seconds it is izoechoic as compared to the cortical area [1]. The "wash-out" phase occurs when the microbubbles disappear from the circulation, the first area that loses the enhancement is the medulla, followed by the cortical "wash-out" [1].

The kidney enhancement intensity and duration depend on the vascular status, the renal flow, the patient's age and, not least, on the performance of the ultrasound machine [1]. Due to the high infusion in the cortical area, high concentrations of UCA are present in the superficial cortical areas that can lead to attenuation, so that the assessment of the deeper areas can be difficult. It therefore recommended that lower doses of UCA should be used to assess renal lesions in low weight individuals with a good ultrasound window (1-1.5 ml SonoVue). To assess the other kidney a new dose of UCA is needed (each kidney is assessed separately).

4. Renal cysts evaluation by means of CEUS

Typically, simple renal cysts appear as well defined, anechoic areas in gray scale ultrasound examination. Sometimes they can be hypoechoic, especially the small ones, being difficult to differentiate from the tumors. Following contrast, even small cysts with hypoechoic appearance on native examination can be visualized, since they do not enhance (they remain black), even during the peak enhancement of the normal renal parenchyma [6]. Thus, CEUS can even elucidate the nature of indeterminate lesions on CT examination (CT contrast agents are excreted by the kidney).

But the true value of CEUS lies in the evaluation of complex renal cysts, type 2F, 3 and 4 according to the Bosniak classification [7,8] (table I), whose nature can not be elucidated by CT or MRI examination. Complex cysts may present irregular thickened walls, thickened septa, wall calcifications, solid components. Enhancement following contrast in any of them demonstrates their vasculature, suggesting malignancy [1].

In a study published in 2007 [9] CEUS assessment was compared to the CT evaluation of 44 complex renal cysts. The study demonstrated a complete interobserver concordance for the CEUS assessment, and a consistent high interobserver concordance ($k = 0.88$) of the CT enhancement following contrast. Also, a complete concordance between CT and CEUS was observed regarding the need for surgery [9].

Another, more recent study (2008) [10], compared the accuracy of CEUS assessment to the gray scale ultrasonography and to contrast CT for the diagnosis in 40 patients with complex renal cysts, the images being inde-

Table I. Bosniak classification of complex renal cysts – adapted from Israel [7].

Type	Category Criteria and Management
1	Benign simple cyst with hairline-thin wall that does not contain septa, calcifications, or solid components. It has water attenuation at CT, anechoic content at US, and does not enhance after contrast agent administration. No intervention is needed.
2	Benign cystic lesion that may contain a few hairline-thin septa in which perceived (but not measurable) contrast enhancement may be appreciated at CT. Few microbubbles of contrast material traveling in the septa may be seen at US. Fine calcification or a short segment of a slightly thickened calcification may be present in the wall or septa. Uniformly high-attenuating lesions (<3 cm in diameter) that are sharply marginated and do not enhance after contrast agent administration are included in this group. No intervention is needed.
2F	Cysts may contain multiple hairline-thin septa. Perceived (but not measurable) enhancement of a hairline-thin smooth septum or wall can be identified at CT. Few microbubbles of contrast material traveling in the septa may be seen at US. There may be minimal thickening of wall or septa, which may contain calcification that may be thick and nodular, but no measurable contrast enhancement is present. There are no enhancing soft-tissue components. Totally intrarenal nonenhancing high-attenuating renal lesions (>3 cm in diameter) that are generally well marginated are also included in this category. These lesions are thought to be benign but need to be followed up to prove their benignity by showing stability.
3	Cystic masses with thickened irregular or smooth walls or septa and in which clear contrast enhancement that is measurable at CT are present. These masses need surgical intervention in most cases, as neoplasm cannot be excluded. This category includes complicated hemorrhagic or infected cysts, multilocular cystic nephroma, and cystic neoplasms. These lesions are diagnosed at histological analysis, as even gross observation by the urologist at surgery or the pathologist at gross pathologic evaluation is frequently insufficient to assign a diagnosis
4	Clearly malignant cystic masses that meet all the criteria of category III cysts but also contain distinct enhancing soft-tissue components independent of the wall or septa. These masses are clearly malignant and need to be removed.

pendently interpreted by three experienced imagists. This study demonstrated the superiority of CEUS as compared to gray scale ultrasound and to CT for the diagnosis of complex renal cysts in all three examiners (83% vs. 30% vs. 75%; 83% vs. 30% vs. 63 %; 80% vs. 30% vs. 70% respectively, $p<0.05$).

5. CEUS for the evaluation of kidney infections

When a severe kidney infection is suspected, especially in patients with renal transplantation, acute pyelonephritis should be differentiated from renal abscess. In B mode, these lesions are sometimes difficult to see as hypoechoic, rarely hyperechoic areas, caused by interstitial edema and/or hemorrhage [11].

In *acute pyelonephritis*, conventional ultrasound has a very low sensitivity (11-40%) for the diagnosis of parenchymal lesions, it is used mostly to exclude complications like hydronephrosis or abscess [12]. The use of color Doppler ultrasound increases the sensitivity (up to 63% in an Italian study) [13]. Power Doppler examination has superior sensitivity and specificity as compared to color Doppler, but it is limited by its low capacity to detect the low flow in small renal vessels [14-16].

Due to the parenchymal edema present in acute pyelonephritis, there is a difference of infusion in the affected parenchyma, which enhances less than the normal one [6], a similar behavior to that observed on contrast CT or in Power Doppler examination [16-18]. A study published in 2007, performed on 100 patients prospectively evaluated by means of CEUS and contrast CT has shown that CEUS has a very good performance for the diagnosis of renal lesions in acute pyelonephritis, with 98% sensitivity, 100% specificity, 100% positive predictive value and 89% negative predictive value [19].

It is well known that sometimes acute renal failure can complicate an acute pyelonephritis (frequently post-transplantation), with the risk of irreversible lesions of chronic pyelonephritis and chronic renal failure (even in patients with unilateral damage) [20]. On the other hand, CT is valuable for the assessment of acute pyelonephritis only if contrast is administered (which is contraindicated in renal failure), and, furthermore, the patient is irradiated. In these circumstances, given the demonstrated good performances of CEUS, perhaps the role of this type of exploration will become increasingly important in the diagnosis of acute pyelonephritis, especially in emergencies, in pregnant women and in children [12,19,21,22].

Regarding the diagnosis of *renal abscess*, conventional ultrasound has a low sensitivity (43%) [4], especially for small abscess, which can distort the renal architecture, but without obvious echogeneity changes [6]. CEUS improves the sensitivity, which can go up to 93% [4]. Renal abscesses do not enhance following contrast, they are usually round, surrounded by a rim that enhances and has a faster wash-out than the rest of the renal parenchyma, the perirenal tissue being usually hypervascular [1,23]. The necrotic, central, avascular abscess area is generally much smaller than the visible hypoechoic hypovascular area visible in B mode, or color Doppler, or Power Doppler examination. This is important to know when trying to perform a percutaneous drainage of the abscess, CEUS guidance improving the chances of success, by targeting the needle strictly in the necrotic area (unenhancing) [4]. Moreover, CEUS examination improves the visualization of abscess extension into the perirenal area [4].

6. CEUS assessment of renal tumors

In renal tumors, due to the neovascularisation, the enhancement pattern is different as compared to the normal capillary circulation of the kidney [5]. Considering this, when a suspected of being a tumor area in conventional ultrasound has a similar behavior with the remaining kidney on CEUS examination, the diagnosis of malignancy can be excluded (the typical case of Bertin pyramids) [6] (fig 2).

Published data suggest that in early stages renal tumors enhance similar to the normal renal parenchyma, sometimes a rim enhancement may be observed [24]. Since the kidneys do not retain the UCA, CEUS seems to be not as valuable as for the evaluation of focal liver lesions. However, since they do not have a capillary bed, kidney tumors will have a faster wash-out than the rest of the renal parenchyma, although less pronounced than in liver [25]. Consequently, renal tumors appear dark (hypoenhancing) in late stages, initially this behavior being detected by the special software of the ultrasound machine, then becoming clear to the subjective assessment of the operator [6].

CEUS evaluation can provide valuable information for the differential diagnosis of hypovascular renal carcinomas, which enhance poorly following contrast on CT examination. Using appropriate software, CEUS is very sensitive for detecting even a small number of microbubbles, thereby detecting tumor vasculature, even when visual assessment of the uptake could lead to doubt [6]. This is true for the detection of intramural blood flow or in the septa of complex cystic lesions, its presence advocating for malignancy [1].

A Japanese study published in 2005 showed a higher sensitivity of CEUS for the diagnosis of hypovascular renal tumors as compared with contrast CT (94.4% vs. 88.9%), while for hypervascular tumors, CT proved to be more sensitive [26].

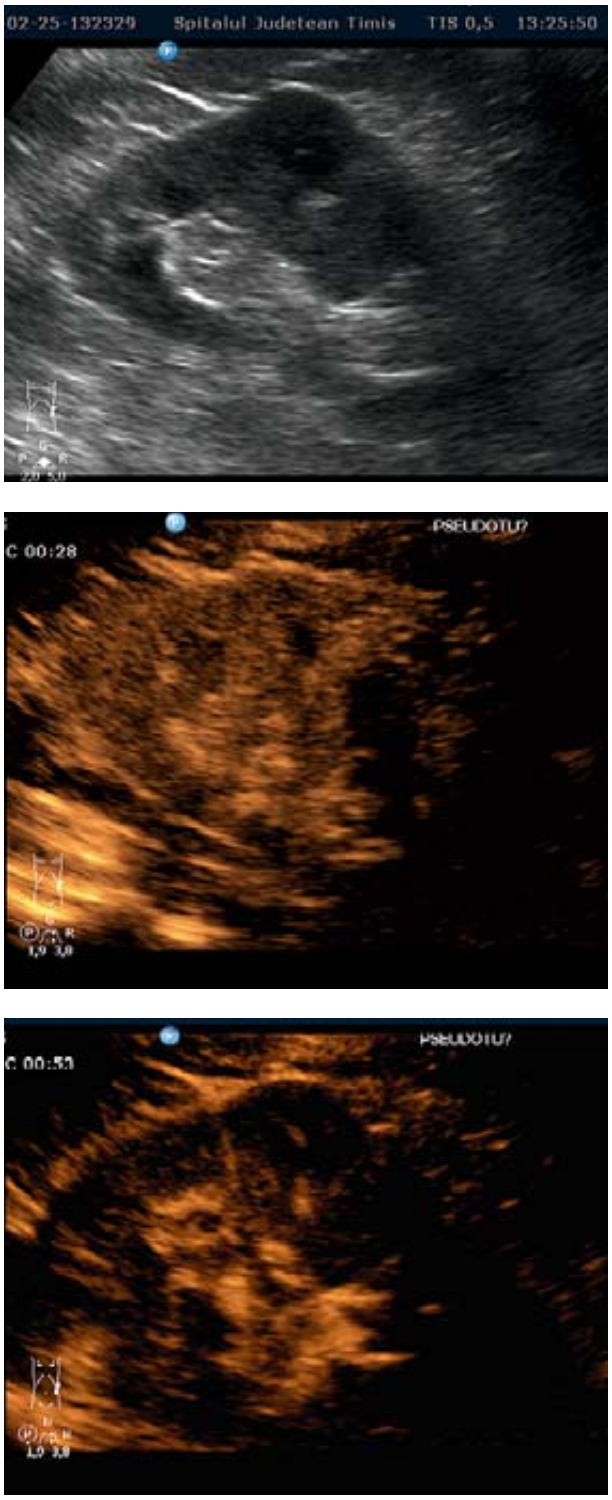


Fig 2. Renal pseudo-tumor. **a.** Standard ultrasound: A hypoechoic mass can be seen in the median area of the left. **b.** CEUS – arterial phase: the mass enhances similarly to the cortical adjacent area. **c.** CEUS – parenchimatous phase: the mass has a similar aspect to the cortical adjacent area.

Also, CEUS evaluation reveals viable lesions (that enhance), thus facilitating the echoguidance in order to obtain adequate bioptic material [27]. CEUS is also useful for evaluating the results of radio frequency ablation in renal tumors, highlighting the presence of viable, enhancing tissue (if any), and for the diagnosis of ablation complications such as bleeding or hematoma, which may mimic a solid renal mass in conventional ultrasound examination [1].

Unfortunately, at present time, CEUS can not distinguish benign vs. malignant renal tumors. There are data suggesting that renal angiolipomas enhance later in the arterial phase than renal carcinomas, the wash-out being also delayed [28] so benign tumors appear hyperechoic in the late phases (fig 3). A recent study showed 100% specificity in differentiating malignant from the benign renal tumors, using as a diagnosis criterion the hypoecogeneity in late phases [29].

7. Applications of CEUS in renal vascular diseases

Depending on the seat of the lesion, renal vascular pathology may be pedicular or peripheral.

7.1. Pedicular renal vascular pathology includes renal artery stenosis, renal artery occlusion and renal vein thrombosis. Also CEUS is useful for preoperative evaluation of renal vessels that intersect the ureter and the basinet, for the corrective surgery of pielo-ureteral junction stenosis [30].

a) Renal artery stenosis. In the diagnostic algorithm of a renal artery stenosis, suspected in the clinical and biological context of a renovascular hypertension, Doppler ultrasound plays an important role, often being the first intention diagnostic method. However, diagnostic efficacy depends largely on operator experience, on method limitation and on a perfect knowledge of diagnostic criteria [31]. Under these conditions, in 10-30% of cases the renal artery can not be an appropriately assessed [4].

Contrast administration improves the performance of Doppler examination, easing the detection of the renal artery and of the optimal location area for Power Doppler examination and also the quality of spectral analysis is improved by reducing the signal/noise ratio. A European multicenter study has shown that by using CEUS, the Doppler assessment failure rate decreased from 36 to 16%, but without a significant improvement in sensitivity and specificity, due to coding artifacts [32-34].

Older studies (1996) reported significant improvement not only regarding the visualization of renal arteries by Doppler examination with Levovist, but also regarding the sensitivity (from 83-85% precontrast to 94-95%

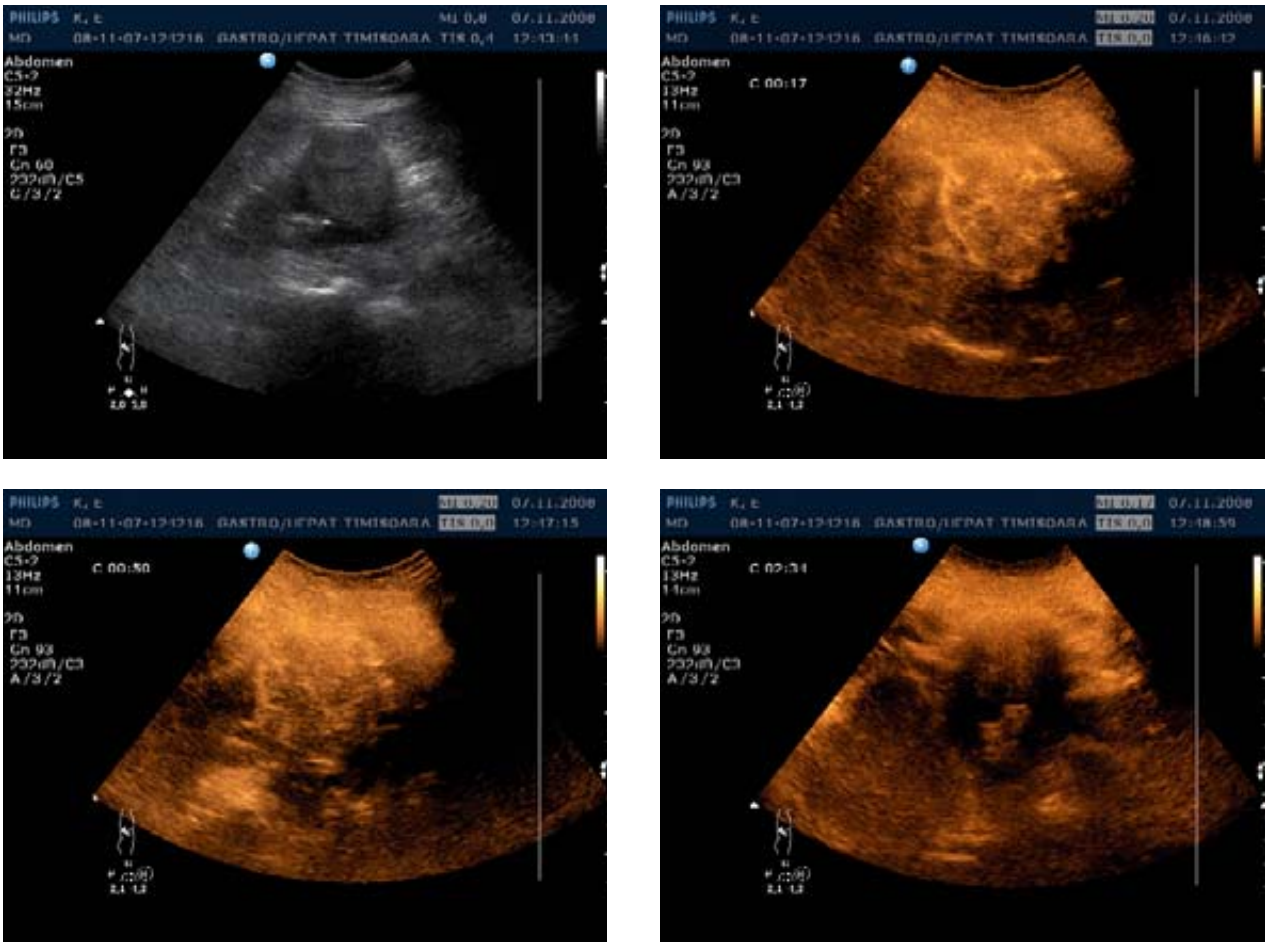


Fig 3. Renal tumor. **a.** Standard ultrasound: A hyperechoic mass can be seen at the upper pole of the right kidney, 4-5 cm in diameter. **b.** CEUS – arterial phase: the mass enhances more than the the cortical adjacent area **c.** CEUS – parenchimatous phase: the mass is hyperechoic as compared to the cortical area and isoechoic as compared to the basinet **d.** CEUS – late phase: the mass is hyperechoic as compared to the cortical area and slightly hypoechoic as compared to the basinet.

postcontrast) and specificity (from 79-81% to 88-93%) for the diagnosis of renal artery stenosis [35,36]. These optimistic data were confirmed by recent studies [37, 38].

In a study in which a 2nd generation UCA was used (SonoVue) in combination with Harmonics and Power Doppler for the diagnosis of renal artery stenosis, it was visualized in all cases, and the sensitivity for the diagnosis of significant stenosis increased from 71 to 93% after SonoVue administration, while the specificity remained at 100% [32].

b) Renal artery occlusion. The diagnostic performance of Doppler ultrasound for the diagnosis of renal artery occlusion is limited by difficulties in optimal viewing of the renal artery starting from its emergence (overweight patient, intestinal loop interposition). The UCA injection improves renal artery visualization, of its anatomic variations [32, 33], and the lack of signal at the ostium confirms the diagnosis of renal artery occlusion [4].

c) The renal vein thrombosis is a difficult diagnosis in standard ultrasound or Doppler examination [4]. UCA administration facilitates renal vein detection, but special attention must be paid when "blooming" occurs, because it can mask the thrombus. In malignant thrombosis arterial enhancement is present [4]. Also, CEUS assessment can provide valuable information after renal transplantation, highlighting postoperative complications like renal artery and/or vein thrombosis [39].

7.2. Peripheral renal vascular disease. An infracted renal area or a cortical necrosis zone will appear as hypoechoic or avascular on Doppler ultrasound [4]. The diagnosis by Doppler ultrasound is difficult if small, superficial renal infarction, also in those situated in areas difficult to visualize, especially post transplantation, when they may coexist with diffuse severe ischemia secondary to acute rejection or to acute tubular necrosis [4].

After UCA administration slow flow areas will be better visualized and infracted areas will be highlighted as avascular, triangular areas [4]. Due to the lack of toxicity and to the fact that UCA are not excreted through the kidney, kidney CEUS can be repeated to track changes that occur over time in the necrotic area [4].

In a recently published study, which compares the diagnostic accuracy of CEUS vs. CT assessment for the diagnosis of renal infarction, very good performances of CEUS were demonstrated, with AUROC 0.992±0.006 and 0.991±0.007 respectively for two ultrasonographists who independently interpreted the images, also with a very good interobserver agreement (kappa=0.83) [40].

8. Vezico-ureteric reflux

Vezico-ureteric reflux assessment is made by transurethral or suprapubic injection of UCA into the bladder. The appearance of the microbubbles in the ureters and in the pelvicalyceal system is followed up, bilaterally, both in B and in Doppler mode [41]. Levovist is currently the only approved UCA for this type of evaluation in children, but preliminary studies performed with SonoVue showed no adverse effects [1].

The sensitivity of CEUS for the diagnosis of vezicoureteric reflux was reported to be 100%, with 97% specificity as compared to retrograde and voiding cystography, being better at grading the reflux, 70% of patients labeled as having stage 1 reflux, having actually stage 2 reflux or over [42].

Gray scale examination after Levovist administration is sufficient for vezico-ureteric reflux detection, but Doppler examination [43, 44] and the use of harmonics [45-47] improve the sensitivity. Also, the urethra can be explored during the voiding, with good diagnostic accuracy [48-50].

By using CEUS, although the examination is slightly longer, the patient is no longer exposed to ionizing radiation (as is the case during retrograde or voiding cystography), hence the possibility of repeating the examination whenever necessary.

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