Eur Radiol Suppl (2004) 14[Suppl 8]:P116–P124
DOI 10.1007/s10406-004-0084-3

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Future prospects for SonoVue and CPS

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Abstract Though long considered unlikely because of the resonance pattern of agents such as SonoVue, high frequency applications for small parts and intracavitary applications now seem very promising. Excellent non-linear signals can be obtained at 7 MHz and higher using recently developed CPS software, and preliminary results suggest that this may prove useful for assessing superficial lymph nodes, the thyroid and parathyroid, breast masses and many superficial masses including those in the skin. Some other potentially useful "fringe" applications of the now-familiar transabdominal transducers with CPS are the pancreas, gall bladder and spleen, though these have not been investigated formally as yet.

Keywords SonoVue · Microbubbles · Small parts · High-resolution ultrasonography

Introduction

The size distribution of the microbubbles in SonoVue (Bracco, Milan), peaking at 2.5 μ (with a corresponding resonant frequency around 4 MHz) suggest that it would not produce useful non-linear signals at the frequencies needed to provide the spatial resolution required for studies of superficial structures and intracavitary uses. However, although when measured by volume of gas the majority of the microbubbles in SonoVue are around 2.5 μ in diameter, there is a substantial tail of much smaller microbubbles which, in terms of numbers, may even dominate the frequency distribution. Thus there is considerable potential for high frequency studies.

Recently, CPS software has been implemented on the Sequoia 15L8 (Siemens-Acuson, Mountain View, CA) probes and experience is beginning to be gathered on its clinical usefulness for superficial structures and for intraoperative scanning. In general, a choice of 7 MHz seems optimal for most small parts, the penetration at 14 MHz being only a few millimetres. However, such a high frequency could be useful for skin lesions and in animal studies, though this has not yet been tested. The dose of SonoVue may need to be on the high side to compensate for the lower sensitivity when working at 7 MHz; 2.4 ml usually required and 4.8 ml is sometimes needed. The MI may also need to be increased a little, 0.3 or 0.4 being optimal. Some examples will be described below.

As well as this exciting new field, there are some fringe applications of SonoVue using the 4C1, 4V1 and 6C2 arrays in CPS mode. For example, the method has been used for pancreatic masses and anecdotal evidence has been presented that the patterns in carcinomas (few vessels) are different from those in focal pancreatitis (vascular). The spleen is another organ where contrast studies are occasionally useful, especially for assessing trauma but also for focal lesions, and here the prolonged retention of SonoVue gives a useful late phase, which is even more intense than in the liver. Transcranial studies of the brain have not yet been reported but this might also prove a useful application, probably using the 4V1 probe and possibly with higher doses of SonoVue.

Small parts studies

Studies in the neck have shown the detailed vascular anatomy, both of the main vessels and of the microvas-

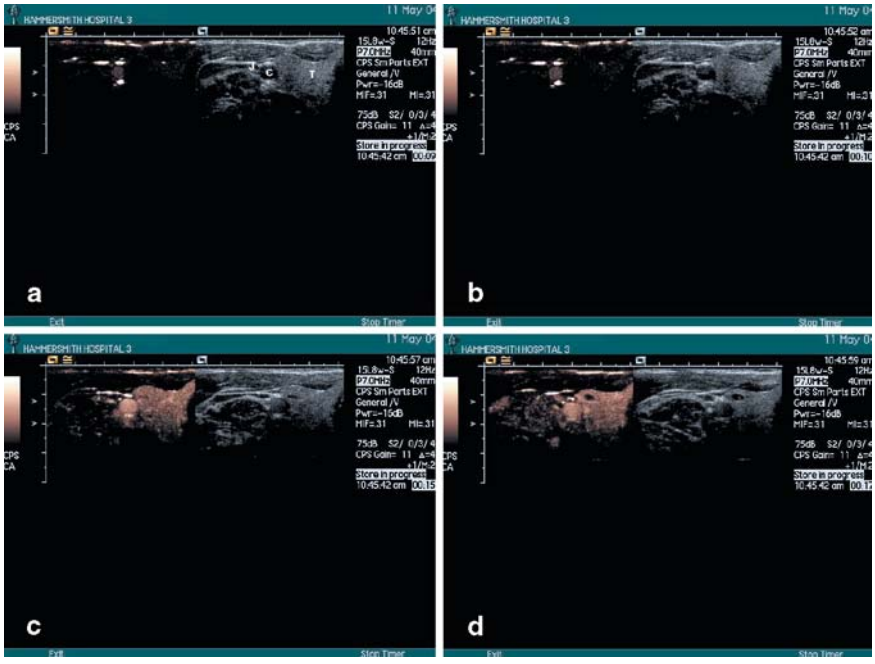


Fig. 1a–d Thyroid nodule. On the image taken 9 s after injection of SonoVue only minor breakthrough signals are seen on the CPS half of the dual screen scan (**a**). Soon afterwards, contrast arrives in the common carotid artery where it shows a linear whorled pattern, which presumably represents the normal helical flow pattern found in all arteries (**b** at 10 s). Then contrast begins to fill the thyroid and a lesion with a distinctive flow pattern is revealed (*arrowheads* in **c** at 17 s) and later a signal free lesion corresponding to a small cystic space on the B-mode scan is clearly seen (**d** at 19 s). The subtle detail revealed by CPS at a frequency of 7 MHz is apparent in this study

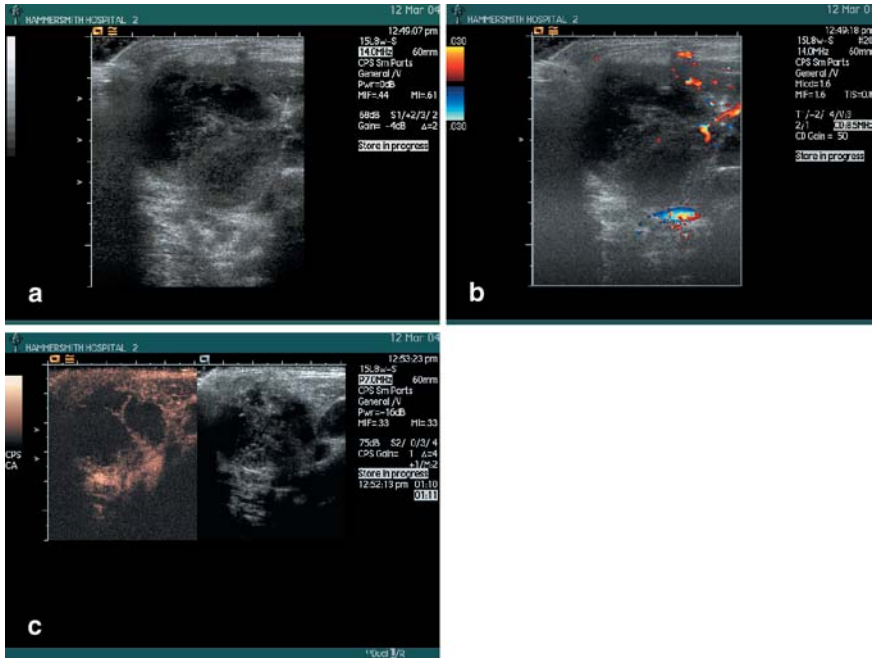


Fig. 2a–c Cervical lymphadenopathy. A large multilobar mass in the neck was found to be a matted group of enlarged lymph nodes with loss of internal structure (**a**) and only weak Doppler signals (**b**). Following administration of SonoVue, the vascular pattern was clearly visualised (**c**) and consisted of a basket-like network outlining the individual nodal masses. Aspiration yielded thick purulent material, which grew mycobacteria on extended culture and the patient was started on an anti-tuberculosis regimen

culature that can be revealed when using CPS at high frequencies with SonoVue. The thyroid is a very vascular structure and it fills uniformly within 30 s of administration of contrast [1] (Fig. 1). Lesions may be highlighted and there is anecdotal evidence that the chaotic arrangement of malignant neovascularisation may be better seen than on Doppler.

Lymph node vascularity can be a useful indicator of activity of lesions, and reports using earlier Doppler techniques with microbubbles have stressed the value of observing their architecture [2-4]. In benign lymphadenopathy the orderly arrangement of the vessels radiating from the nodes' hila tends to be preserved while in metastatic lymphadenopathy not only is the arrangement chaotic but also new vessels can be identified penetrating the node's capsule. However, in aggressive inflammation, there may be so much necrosis that these features are difficult to recognise (Fig. 2).

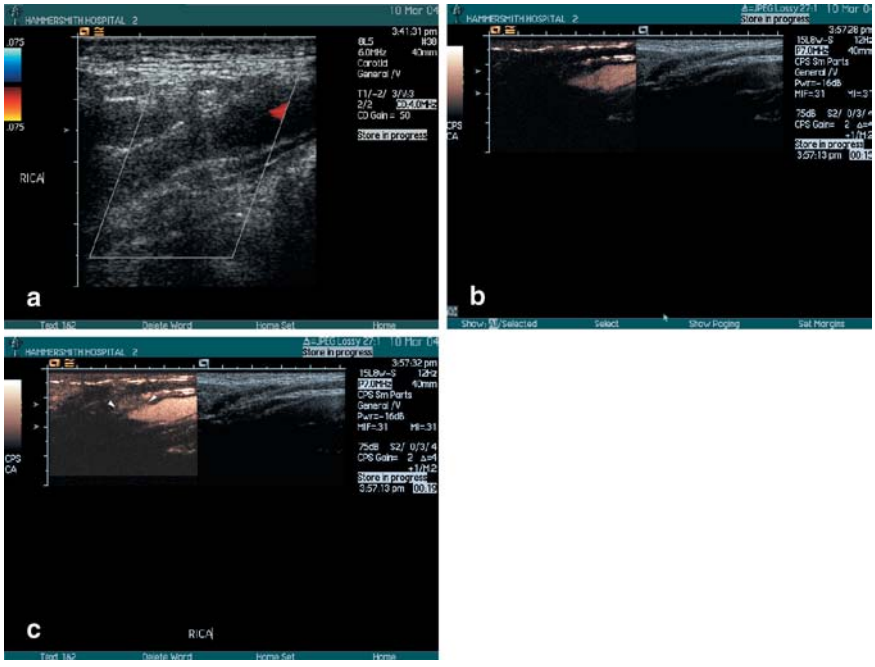


Fig. 3a–c Neovascularisation in carotid atheroma The contrast scan was performed to exclude trickle flow in this patient with an apparent total occlusion on Doppler (**a**). Fifteen seconds after the injection and using CPS at 7 MHz the impression that the internal carotid artery was completely occluded was confirmed (**b**). Four seconds later, minute but discreet vessels could be discerned within the plaque (*arrowheads* in **c**). These are new vessels recruited by the atheroma from the arteries vasa vasorum. Neovascularisation defines a critical phase in plaque evolution after which they become more unstable and likely to become symptomatic

An intriguing observation is the possibility of demonstrating the neovascularisation within atheromatous plaque (Fig. 3). These are vessels recruited to supply the plaque from the host arteries' vasa vasorum and their development is a critical stage in the formation of plaque because they supply the majority of the lipids that accumulate as atheromatous deposits [5]. Vascularised plaques are more unstable than fibrous plaques and therefore more liable to rupture or ulcerate, with attendant emboli leading, for example, to strokes. These minute vessels can be observed as thread-like, moving lines within the plaque.

Much has been published on the use of older contrast ultrasound methods to assist in the differentiation between benign and malignant breast masses [6, 7]. High frequency CPS with SonoVue is effective in the breast where the malignant neovasculature of cancers is well shown with high spatial resolution. Since breast cancers that are highly vascular have a worse prognosis with earlier invasion and metastases, their identification could have major clinical implications [8]. Ultrasound might be better than histological examination because it can cover the entire lesion and so is less subject to sampling error underestimation. An allied use might be in assessing the vascular component of their response to systemic treatment using either more conventional antitumour drug regimens or using the newer anti-angiogenesis agents. A direct demonstration of the effectiveness of such treatment might be of great value in monitoring response. A practical use of SonoVue in the breast is in increasing confidence that a lesion is benign by demonstrating lack of vascularisation (Fig. 4).

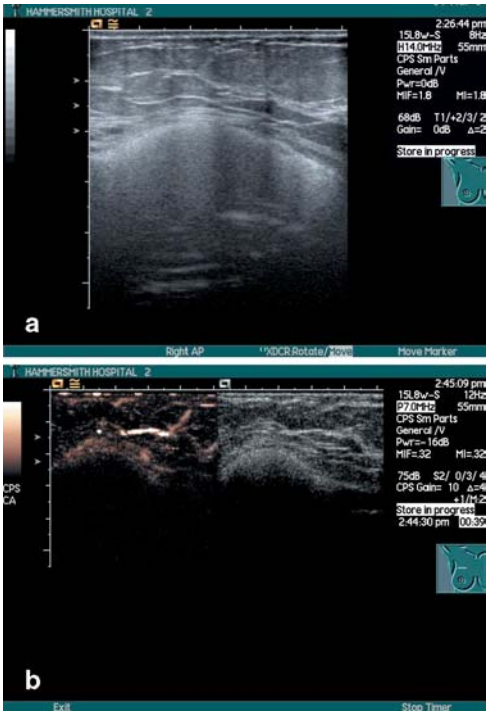


Fig. 4a,b Silicon breast prosthesis. Lumpiness around this breast prosthesis raised a concern about incidental malignancy and the patient was referred for ultrasound, which revealed the typical snowstorm pattern of granuloma formation around a silicon leak (**a**). No Doppler signals were obtained from it and a contrast study was offered to increase confidence that the lesion was entirely fibrous. The CPS scan after SonoVue showed the expected enhancement in the surrounding breast, mainly running along the Cooper's ligaments, but only a faint blush at the margin of the granuloma, making malignancy very unlikely (**b**)

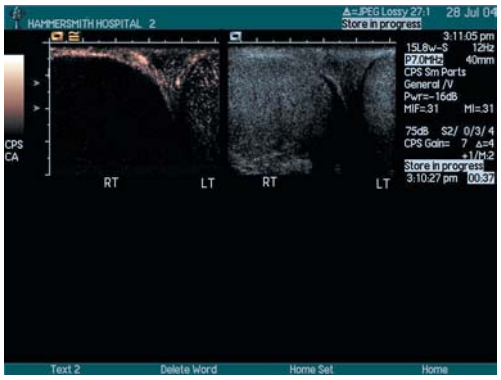


Fig. 5 Testicular infarction. This unfortunate patient suffered scrotal pain after a right inguinal hernia repair. Instead of the expected haematoma or features of inflammation, a testis with inhomogeneous echogenicity and no Doppler signals was found. The head of the epidydimus was also enlarged and devoid of Doppler signals. Because of the unusual story and the seriousness of the proposed diagnosis of testicular infarction, a contrast study was performed with SonoVue and CPS on the 15L8W transducer. The left testis and the scrotal wall showed good enhancement, but the right testis remained devoid of signals supporting the diagnosis of infarction, which was proven at subsequent surgery

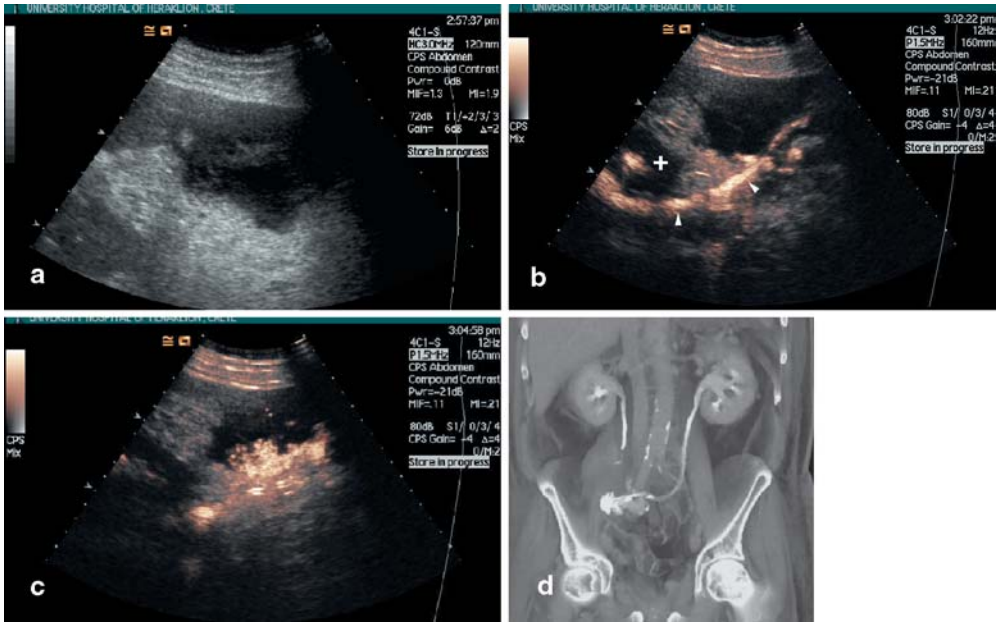
Fig. 6a–d Ultrasound nephrostogram. Following radical cystectomy for a bladder carcinoma, with fashioning of an ileal conduit, this 61-year-old man developed flank pain. The right kidney was found to be hydronephrotic and a nephrostomy was performed. A fluid collection was found overlying the right psoas muscle (**a**). To evaluate whether it communicated with the conduit, diluted SonoVue (2.4 ml in 60 ml saline) was instilled into the nephrostomy tube and the region of the collection was scanned in CPS. Contrast could be demonstrated in the renal pelvis (+ in **b**), in the conduit (*arrowheads*) and spilling into the collection (*arrowhead* in **c**), indicating that this was a leak from the anastomosis. The findings were confirmed on a CT nephrostogram (**d**). (Case kindly contributed by Dr. S.D. Yarmenitis, University of Crete)

Generally testicular scanning with Doppler is adequate for evaluating vascularisation, but where there is continuing doubt, enhancement with SonoVue and examination under CPS may give increased confidence (Fig. 5).

Skin scanning with very high frequency systems (20 MHz or higher) is gradually becoming accepted as a useful improvement even over expert visual diagnosis of pigmented naevi, to determine those that are suspected of being malignant and therefore need biopsy [9]. Demonstration of vascularity using Doppler forms part of this assessment. There is no report of the use of microbubbles in this application, but the ability to use the 15L8 probe in CPS mode at frequencies up to 14 MHz makes this a promising concept.

Abdominal studies – Large vessels and non-vascular studies

While the focus of interest of using SonoVue with CPS is the microvasculature, there continue to be important uses in large vessels, many of which have been referred to in other articles in this supplement, e.g., aortic aneurysms and vascular problems in the liver. Another example is in renal artery stenosis, where they are used in the way that ultrasound contrast agents were originally envisaged, to rescue a failed study and obtain useful signals from otherwise inaccessible vessels. An advantage of using CPS here is the lack of motion artefact so that the vessels stand out more clearly and the image can be used to guide placement of the spectral Doppler gate. While no studies using SonoVue with CPS have been published, there are reports of the use of Levovist (Schering,



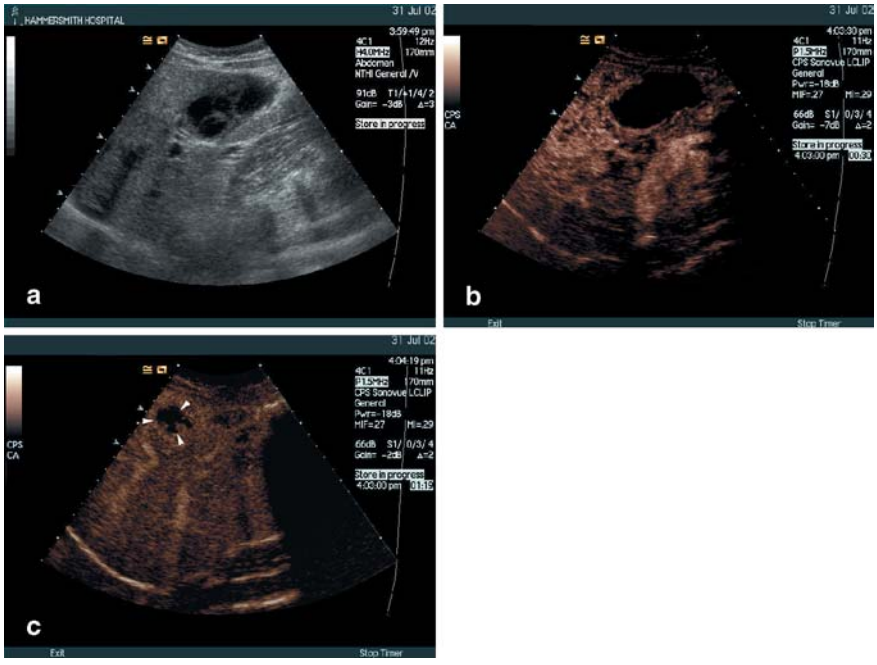


Fig. 7a–c Right upper quadrant pain after hepatic artery embolisation. This patient's symptomatic carcinoid syndrome was treated by hepatic artery embolisation. A few days later she developed right upper quadrant pain and was referred to ultrasound to assess the possibility that the cystic artery might have been inadvertently occluded, leading to gall bladder infarction. On B-mode, the gall bladder wall was thickened and it contained echogenic material (**a**); no Doppler signals could be obtained, but exclusion of gall bladder infarction was important because of the serious consequences of bile peritonitis if it ruptured. Following enhancement with SonoVue, good perfusion of its entire wall was demonstrated (**b**) and, in the sinusoidal phase when the liver parenchyma enhanced, a subcapsular metastasis was identified (*arrowheads* in **c**); presumably this was the cause of her pain. She was managed conservatively and did well

Berlin) with Doppler, and this makes the study faster to perform and gives the reader more confidence in the result [10]. Perhaps surprisingly, it did not improve accuracy.

Levovist has been licensed in some European countries (notably Germany) for use in vesico-ureteric reflux where it is at least as sensitive as conventional micturating cystography and can avoid exposure to ionizing radiation, especially for follow-up studies [11]. SonoVue has not been licensed for this type of application but, given its isotonicity and inert nature as well as its strong non-linear behaviour, it would seem to be eminently suitable. SonoVue with CPS has been tried with success as an alternative to X-ray nephrostograms (Fig. 6).

Abdominal studies – The microvasculature

One of the more intractable diagnostic challenges in gastro-enterology is the distinction between a carcinoma of the head of the pancreas and chronic focal pancreatitis. They often have indistinguishable imaging appearances and even biopsy can be difficult because cancers may produce a marked fibrotic (desmoplastic) reaction such that the amount of fibrous tissue can outweigh the amount of malignant tissue. Reports that contrast-enhanced ultrasound can aid with this differential by highlighting the vascularisation of pancreatitis by comparison with the lack of vascularisation in carcinomas are therefore of great interest [12-14].

The biliary tree may seem an unlikely application for contrast enhancement but there are instances where Doppler is not definitive and SonoVue with CPS can solve a problem. Examples include suspicion of gall bladder infarction (Fig. 7) and in the assessment of the vascularity of a gall bladder mass (Fig. 8). It has also proved helpful in establishing that a filling defect in the common bile duct is a soft tissue mass and not biliary sludge (Fig. 9).

The spleen, like the liver, has a long duration of enhancement with SonoVue and, even more than the liver, the slope of its washout is flatter, suggesting that there is true splenic tropism. Its site of accumulation has not been established and may simply be passive pooling in the large vascular spaces of the spleen. This property has been found useful in trauma and it also helps in characterising focal splenic lesions. Haemangiomas, though rare in the spleen, have the same haemodynamic sequence (peripheral clumping followed by gradual centripetal filling) as is seen in the liver, while malignancies appear as rounded defects and infarcts as wedge-shaped defects. In the early arterial phase, splenic enhancement may be heterogeneous with striking geographical defects just as on

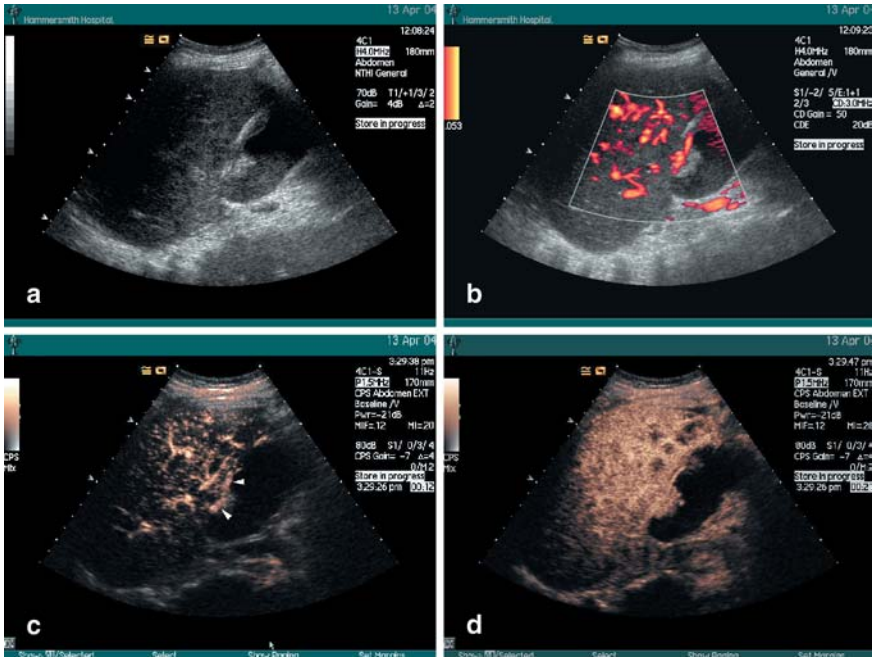


Fig. 8a–d Gallbladder carcinoma. This patient presented unwell and with upper abdominal pain. On grey-scale scanning the liver was noted to be heterogeneous and there was a mass in the gall bladder, as well as debris (**a**). Doppler suggested that the mass was somewhat vascular (**b**) but, after administration of SonoVue, it was seen to be very vascular, enhancing in the arterial phase and increasing over several seconds (**c** at 12 s, **d** at 21 s). The heterogeneity of the liver turned out to consist of a myriad of late phase defects. The final diagnosis was carcinoma of the gall bladder with metastases

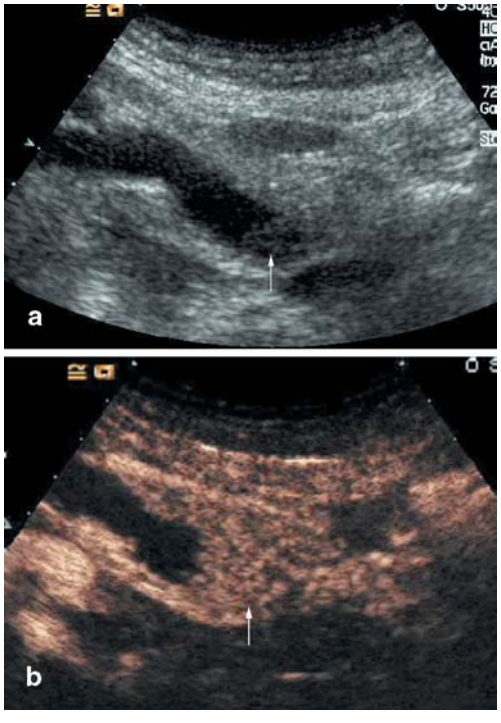


Fig. 9a,b Painless jaundice. This 78-year-old man presented with painless jaundice and the ultrasound scan showed intra- and extrahepatic bile dust dilatation. The common bile duct could be traced down to the head of the pancreas where poorly reflective material could be visualised within the duct (*arrow* in **a**). In order to differentiate between echogenic bile debris and a mass, 2.4 ml of SonoVue was given i.v. and 24 s later the region showed clear enhancement (*arrow* in **b**), indicating that it was a soft tissue mass. Papillary carcinoma was found at surgery. (Case kindly contributed by Dr. S.D. Yarmenitis, University of Crete)

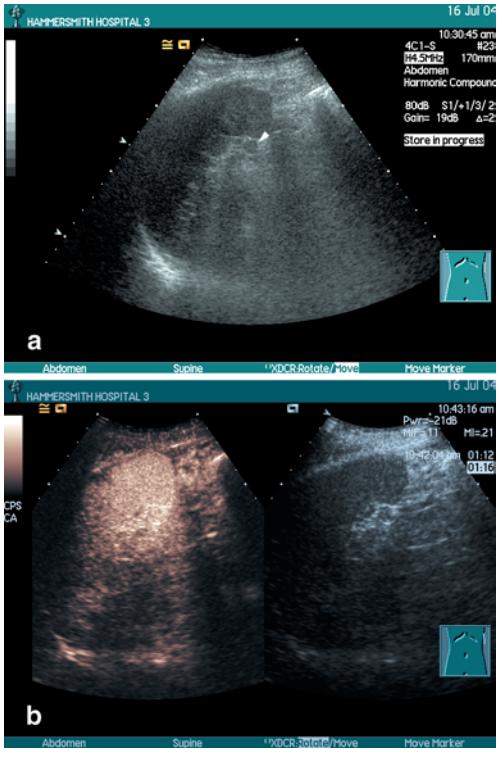


Fig. 10a,b Splenunculus. A rounded mass was found adjacent to the spleen in this patient with abdominal pain (*arrowhead* in **a**). It has features of a splenunculus but could represent an abnormal lymph node. A minute after injection of SonoVue, it filled with contrast (**b**), making a firm diagnosis of an accessory spleen. CPS was used in live dual mode so that the suspect region could be kept in view on B-mode, thus allowing confident identification of the splenunculus

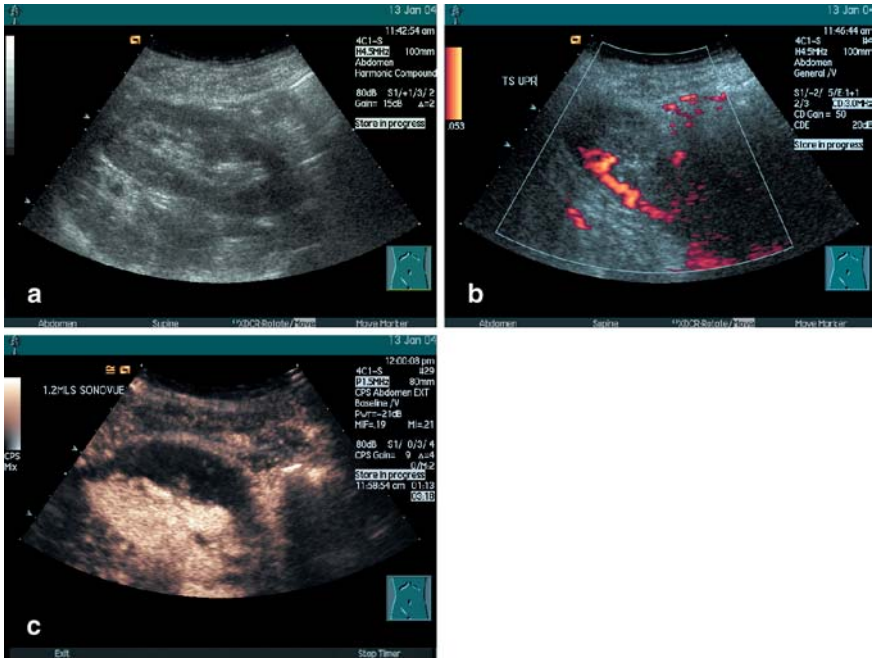


Fig. 11a,b Renal transplant infarct. Following a difficult anastomosis, an ultrasound assessment of the arterial supply of this renal transplant was requested. On B-mode the kidney appeared normal (**a**) but only poor Doppler signals could be obtained from it (**b**). Following SonoVue injection, the main renal artery enhanced well, as did the deeper part of the kidney but the remaining two thirds showed no enhancement. The transplant eventually failed and had to be removed. The lack of nephrotoxicity of SonoVue makes it particularly useful in this application

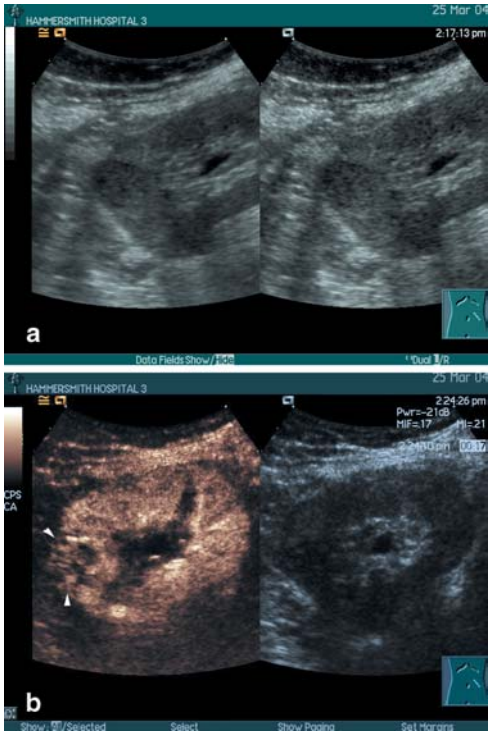


Fig. 12a,b Mass on a transplant kidney. An equivocal mass was noted in a routing follow-up scan of this patient with a transplant kidney (**a**). No interpretable signals were seen on power Doppler and so contrast was administered. This confirmed the suspicion of a mass by showing non-uniform perfusion of the kidney with later arrival in the upper pole than in the remainder of the cortex (*arrowheads* in **b**). Contrast-enhanced ultrasound can often help distinguish artefactual lesions and developmental anomalies from malignancies, most of which are vascular

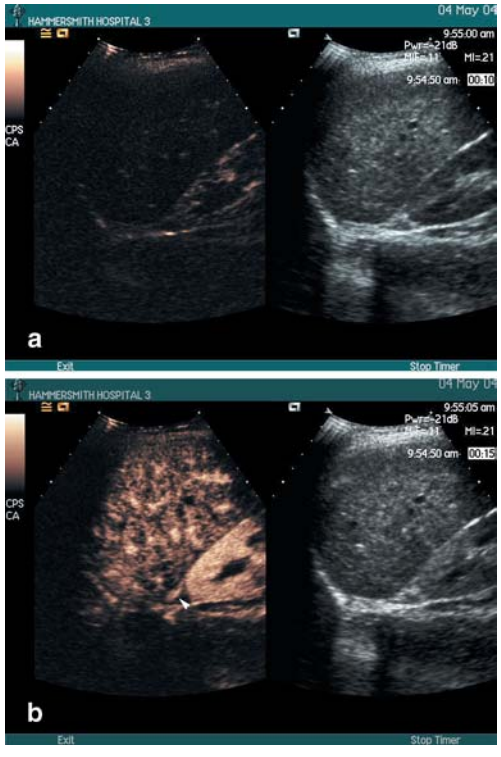


Fig. 13a,b Adrenal gland. The adrenal gland is not seen on the baseline of this split-screen CPS display (**a**) but fills at the same time as the renal cortex and the arterial phase in the liver (*arrowhead* in **b**, at 15 s after injection). The excellent spatial resolution of CPS with SonoVue allows such detail to be displayed

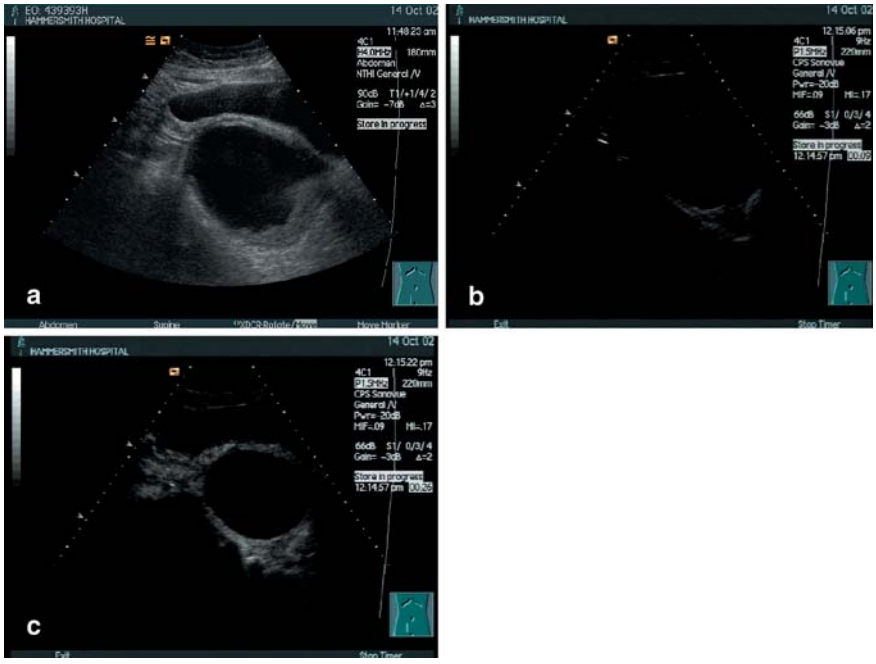


Fig. 14a-c Ovarian cyst. The wall of this ovarian cyst was considered suspicious on a transabdominal scan (**a**) and so SonoVue was administered. In CPS mode, no signals were obtained initially (**b**) until the arrival of the microbubbles and, 26 s after the injection the CPS study shows uniform enhancement around the cyst wall (**c**), which intensified over the next few seconds. The lack of focal enhancement or flow in the mural nodule was considered reassuring and the cyst was followed: it disappeared on a repeat scan 6 weeks later

CT, and this makes interpretation difficult in the early phases; after this, uniform enhancement should be seen with CPS. Caution should be exercised in interpreting apparent defects during the first minute or so after injection.

Splenunculi, common normal variants, can be confusing on unenhanced scanning as they may be confused with lymphadenopathy at the splenic hilum (Fig. 10). CPS (or agent detection imaging, ADI) a couple of minutes after a dose of SonoVue can solve this problem: splenunculi take up and retain contrast while lymph nodes show only transient enhancement in the arterial phase [15].

Assessment of the integrity of the vascular supply to transplanted kidneys is a valuable application of SonoVue with CPS, especially as it is not nephrotoxic, a limitation of iodinated X-ray contrast agents (Fig. 11). It can also be used to clarify equivocal lesions, just as in the native kidneys (Fig. 12).

The adrenal glands are normally very vascular (Fig. 13) and it is to be expected that abnormalities will be described in adrenal pathologies.

Another promising area of application is in gynaecology, where reports of older techniques suggest that contrast-enhanced ultrasound may help in distinguishing benign from malignant adnexal masses (Fig. 14) [16]. If substantiated, this would be an important advance because currently all women presenting with a complex or solid adnexal mass need surgery (laparoscopy or laparotomy) but some 75% of these lesions turn out to be benign. A test that improved this separation would save many unnecessary explorations.

Conclusions

While it is clear that the liver will continue to be the most important application of SonoVue with CPS, there are many other fields where it is or is likely to prove a valuable diagnostic tool. The provision of CPS for small parts scanning promises a new group of applications that are only just being explored.

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