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Assessment of Vascular Perfusion Kinetics Using Contrast-enhanced Ultrasound for the Diagnosis of Prostatic Disease in Dogs

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Contents

Vascular perfusion was assessed in 10 dogs without prostatic abnormalities and 26 dogs with prostatic disease using contrast-enhanced ultrasound. The time to reach peak contrast intensity (TTP) and peak perfusion intensity (PPI) were measured, and histological biopsies were collected from each dog. Biopsies confirmed normal prostate (n = 10), benign prostatic hyperplasia (n = 11), mixed benign pathology (n = 9), prostatitis (n = 1), prostatic malignancy [adenocarcinoma (n = 4); leiomyosarcoma (n = 1)]. In normal dogs, mean PPI was 16.8% ± 5.8 SD, and mean TTP was 33.6 ± 6.4 s. Benign conditions overall were not statistically different from normal dogs ($p > 0.05$); for benign prostatic hyperplasia, mean PPI was 16.9 ± 3.8%, and mean TTP was 26.2 ± 5.8 s; for mixed benign pathology mean PPI was 14.8 ± 7.8%, and mean TTP was 31.9 ± 9.7 s; for prostatitis, PPI was 14.2%, and TTP was 25.9 s. The malignant conditions overall had perfusion values that differed from the normal dogs ($p < 0.05$), although evaluation of the data for individual malignancies did not demonstrate a consistent trend; for adenocarcinomas, the PPI was numerically higher with a mean of 23.7 ± 1.9%, and the mean TTP was 26.9 ± 4.8 s, whilst for the dog with leiomyosarcoma values were numerically lower with a PPI of 14.1% and TTP of 41.3 s. Contrast-enhanced ultrasound appears to offer some ability to document differences in perfusion that may differentiate between malignant and benign lesions, although studies with larger numbers of animals are required to confirm this contention.

Introduction

Prostatic disease is frequently seen in small animal practice. The most common conditions affecting the canine prostate include benign prostatic hyperplasia, prostatitis, prostatic cysts and prostatic neoplasia (Smith 2008). Unfortunately, the diagnosis of malignant prostate disease is challenging because benign and malignant lesions may, at least initially, have a similar clinical and imaging appearance (Jemal et al. 2007).

In men may also develop a similar spectrum of prostatic diseases and as much the medical literature is worthy of review and prostate cancer is the most frequently diagnosed cancer and is a leading cause of cancer death (Culty and Richard 2006). The diagnosis of prostate cancer in men is made on histological biopsy results. The decision whether or not to take biopsies is dependant on prostate-specific antigen (PSA) levels, digital rectal examination and transrectal ultrasound findings. However, the value of each of these investigations is limited (Mitterberger et al. 2007). The optimal PSA cut-off level is not yet determined neither is the optimal number of biopsies required to obtain a diagnosis (Norberg et al. 1997; Djavan et al. 2000; Shah et al. 2005; Eichler et al. 2006). The search for improved diagnostic techniques continues, and a variety of other imaging modalities have been reported in human medicine, including computed tomography, magnetic resonance imaging, positron emission tomography and single photon emission computed tomography (Fuchsjäger et al. 2008; Delgado Bolton et al. 2009; Deutscher et al. 2009; McMahon et al. 2009; Weinreb et al. 2009). Contrast-enhanced ultrasound (CEUS) has been reported to be useful for the differentiation of human prostate cancer from other non-malignant conditions (Mitterberger et al. 2007; Wink et al. 2008). Using CEUS, a bolus of contrast agent is injected intravenously and then the gland monitored to measure accumulation of the contrast. The analysis of ultrasound contrast agent bolus kinetics yields various time-intensity curve parameters that qualitatively describe regional perfusion. Peak perfusion intensity (PPI) is expressed as a percentage of background intensity, and the time to reach peak intensity (TTP) is expressed in seconds from the time of injection. These values are representative of different aspects of vascularization of the region of interest (ROI).

In the dog, prostatic carcinoma is a highly malignant neoplasm with a prevalence of 0.2–0.6% (Weaver 1981). Prostatic neoplasia must be distinguished from non-malignant prostatic disease so that appropriate treatment can be initiated. One recent study reported that the presence of mineralization in the prostate identified with either abdominal radiographs or ultrasound is considered highly suspicious for prostatic neoplasia (Bradbury et al. 2009). Prostatic mineralization is considered even more suspicious for neoplasia if the dog is neutered (Bradbury et al. 2009). However, other studies have reported that mineralization also occurs in chronic bacterial prostatitis, benign prostatic concretions (calculi) and prostatic abscess (Feeney et al. 1987; Burk and Ackerman 1996). In the dog, there have been few investigations of the plethora of imaging modalities used in humans, and ultrasonography is considered to be the imaging modality of choice for evaluation of the prostate gland. Unfortunately, despite providing excellent images, it may be difficult to differentiate between benign and malignant canine prostatic diseases with ultrasound because of their similar appearance when using this technique (Mahaffey et al. 1995), and specific colour-flow Doppler patterns have not been described for the different prostatic conditions. A recent study

reported the normal prostatic and urethral perfusion values in dogs (Russo et al. 2009). Normal values for PPI ranged between 15.5% and 17.6%, depending on the view (longitudinal or transverse) and on the side (right or left), whilst for TTP ranged between 29.9 and 37.5 s.

The aim of this study, which we believe is the first in veterinary medicine to describe the use of CEUS in dogs with prostatic disease, was to evaluate the perfusion kinetics in dogs without prostatic abnormalities and those with prostatic disease confirmed histologically as being benign or malignant.

Materials and Methods

Ten dogs without prostatic abnormalities (mean age of 2.2 ± 0.9 SD years), and weighing between 6 and 37 kg and 26 dogs with prostatic disease (mean age of 9.3 ± 2.3 SD years), and weighing between 7.5 and 43.0 kg were included in this study. Ethical approval for the study was gained through the normal procedure of the University of Naples. Dogs were examined at the Veterinary Clinic dell'Orologio; 20 dogs were referred with clinical signs unrelated to prostatic disease, whilst six were referred for tenesmus, haematuria, stiff gait and/or anorexia.

After physical examination, all dogs were evaluated with abdominal radiographs, serum chemistry profile, complete blood cell count and urinalysis (data not shown), before ultrasonography was performed.

This study used the technique previously reported by Russo et al. (2009). A 20-G intravenous cannula was placed in the cephalic vein. All patients then underwent general anaesthesia with diazepam 0.2 mg/kg i.v. and propofol 4 mg/kg i.v., which was given until tracheal intubation was possible. Anaesthesia was maintained with isoflurane (1–3% in oxygen), and intravenous saline was administered throughout the procedure. All dogs were maintained in right lateral recumbency and haemoglobin oxygen saturation, heart rate, blood pressure and CO_2-saturation were monitored continuously throughout anaesthesia.

Ultrasound examination of the caudal abdomen was performed with a 5–7.5 MHz linear transducer with coded harmonic capability (Mylab 30, Esaote-CnTI System; Esaote, Genova, Italy).

Maximum prostatic width was measured in the transverse plane, and a colour Doppler examination was performed at a rate of 0.7–1.4 frames per second. Once a focal or diffuse prostatic lesion was identified in the dogs with prostatic disease the contrast study was then undertaken.

A second-generation contrast agent SonoVue (Sulphur hexafluoride microbubbles; Bracco Imaging S.p.A., Milan, Italy) and a dedicated CEUS analytical software (Contrast Tuned Imaging – CnTI™-Contrast Tuned Imaging Technology; Esaote) were used. The mechanical index was always lower than 0.1 (range 0.05–0.1) to reduce the acoustic impact of the ultrasound waves on the micro bubble contrast agent, and to increase the persistence of the contrast medium in the blood. A single focal zone was placed in the deepest part of the prostate. The overall gain and time-gain compensation were set so that no signal from the prostatic parenchyma was present, and only a very low background signal from the prostatic capsule was maintained to ensure an anatomic reference in the image. The contrast medium was injected into the cephalic vein at a dose of 0.03 ml/kg of prepared solution (5 mg/ml) followed by a rapid bolus of 5 ml of saline solution. The timer was activated at the moment of starting the injection (T0), and the flow of contrast medium into the prostate gland was observed in real-time. Care was taken to keep the ultrasound transducer in exactly the same position for at least 1.5 min. The entire examination was digitally recorded. Thereafter, a single transabdominal ultrasound-guided Tru-Cut biopsy of a random portion of the gland (dogs without prostatic abnormalities) or a targeted biopsy (dogs with prostatic disease) was taken using a 16-G spring-loaded biopsy needle (Russo et al. 2009).

All the recorded videos were reviewed, and the enhancement pattern was subjectively described. A commercial software application (QONTRAST, Milan, Italy) was then used to construct time-intensity curves. A frame was selected every 10 s for the first 1.5 min of the videos. For focal prostatic lesions, a ROI was manually drawn in each area considered to be abnormal. In cases of diffuse prostatic lesions, two ROIs were drawn. For all of these, the best image possible was chosen, either in a longitudinal or transverse plane. Random ROIs were selected for the normal dogs. The PPI (expressed as a percentage) and the TTP (expressed in seconds) were calculated from T0.

All values were calculated as mean and median (±SD) and reported descriptively for each of the histological classification groups. For prostatic width, comparisons were made between values for normal dogs ($n = 10$) with dogs with prostatic disease ($n = 26$); whilst for perfusion parameters, comparisons were made between normal dogs ($n = 10$), dogs with benign lesions ($n = 21$) and dogs with malignant lesions ($n = 5$). Data were not normally distributed and therefore, non-parametric analysis was performed using the Welch's t test (GraphPad Software, Inc., San Diego, CA, USA); values were considered to be significant when $p < 0.05$.

Results

Prostatic biopsy was successfully performed in each case without adverse effects. Histopathological examination of the biopsies demonstrated normal prostate ($n = 10$), benign prostatic hyperplasia ($n = 11$), prostatitis ($n = 1$), prostatic malignancy [adenocarcinoma ($n = 4$); leiomyosarcoma ($n = 1$)] and mixed benign pathology ($n = 9$). The latter cases included benign prostatic hyperplasia together with either prostatitis or metaplasia.

For the 10 normal dogs, B-mode ultrasound demonstrated a homogenous moderately hyperechoic parenchyma and a prostatic width between 2.0 and 3.5 cm. In each of the 26 abnormal dogs, prostate width was larger than published values for body size (Atalan et al. 2008), and actual prostatic width was between 3.5 and 8.5 cm; prostatic width differed significantly for dogs without prostatic abnormalities compared with those with prostatic disease. The most common findings in

cases of benign prostatic disease (hyperplasia, prostatitis, mixed pathology) were a heterogenous parenchyma (16 cases) (of these 11 cases also had cystic lesions). In the remaining five cases, there was only prostatomegaly with a homogenous parenchyma. In one case of prostatitis, peri-prostatic free fluid was visible ventrocranially. When the prostate was very large, there was a progressive decreasing echogenicity of the organ in the far field sometimes making imaging very difficult.

In the four cases of prostatic adenocarcinoma, mild to marked mineralization of the prostatic gland was observed. In the one case with prostatic leiomyosarcoma, a well-defined hypoechoic area was documented. The latter was always hypoechoic compared with the surrounding parenchyma also during the contrast study, during the wash in, at the peak, and the wash out phases (Fig. 1).

In each dog, the contrast study was effectively performed without adverse effects. The major difficulties encountered were associated with artefacts because of mineralization, often causing distal acoustic shadowing, making imaging of the distal part of the prostate gland almost impossible (Fig. 2). In cases of severe prostatomegaly, it was not possible to display the entire gland in the field with the 7.5 MHz linear probe, and with the 2.5–3.5 MHz convex transducer there was a severe loss of resolution. Another observation was that several, small cyst formations could alter the curve value calculations because of non-enhancing areas within the ROI.

For the normal dogs, the PPI was a mean of 16.8% (±5.8 SD) with a median of 17.80%. The mean TTP was 33.6 ± 6.4 s with a median of 34 s.

For dogs with benign conditions, there were no statistical differences ($p = 0.12$) to values for the normal dogs. For benign prostatic hyperplasia, the PPI was a mean of 16.9 ± 3.8% (median 15.8%), and the TTP was a mean of 26.2 ± 5.8 s (median 24.4 s). For mixed benign pathology, the PPI was a mean of 14.8 ± 7.8% (median 12.2%), and the TTP was a mean of 31.9 + 9.7 s (median 32.8 s); for prostatitis, the PPI was 14.2%, and the TTP was 25.9 s.

For the four dogs with adenocarcinomas, values were significantly higher ($p < 0.05$) than the normal dogs; the PPI was a mean of 23.7 ± 1.9% (median 24.2%), and the TTP was 26.9 ± 4.8 s (median 21.1 s). For the dog with the leiomyosarcoma, values were not compared statistically but were numerically lower than in the normal dogs; the PPI was 14.1, and the TTP was a mean of 41.3 s.

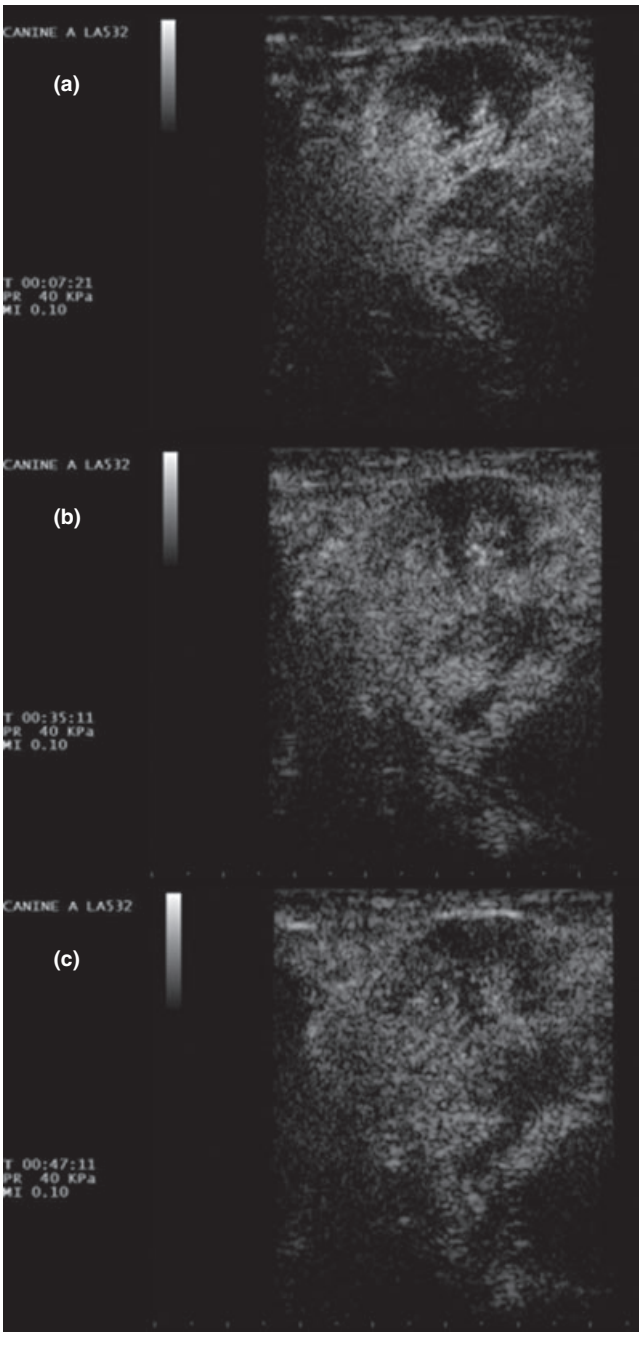

Fig. 1. Contrast-enhanced ultrasound of a 6 year old, Jack Russell Terrier dog with a final diagnosis of leiomyosarcoma. Early wash in phase (a), late wash in phase (b) and early wash out phase (c), respectively, 7, 35 and 47 s after contrast medium injection. Time to reach peak intensity was a mean of 41.3 s. In all the phases of the study, the lesion was hypoechoic compared with normal surrounding tissue

Discussion

Imaging the prostate gland of dogs with prostatic disease is common within clinical veterinary practice. Unfortunately, however, there is a lack of specificity of the ultrasonographic characteristics of different conditions of the prostate, making their differentiation difficult (Mattoon and Nyland 2002). In this study, we were also unable to demonstrate specific ultrasonographic features characteristic of different types of prostatic pathology. Furthermore, even using colour Doppler ultrasound, it was not possible to distinguish between benign or malignant lesions. However, B-mode ultrasound was useful in allowing measurement of prostatic dimensions as well as the documentation of cystic lesions and para-prostatic changes including the presence of peritoneal fluid.

Although prostatic pathology in dogs differs to the disease observed in men, it is worthy of note that in human medicine, trans-rectal imaging of the prostate using CEUS is a well-established technique used in

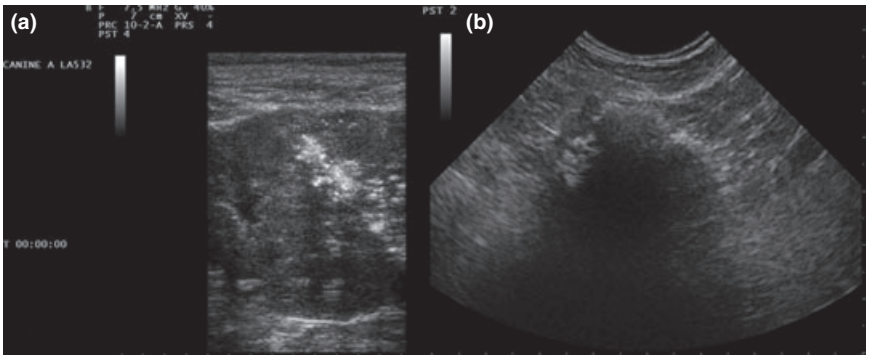

Fig. 2. B-mode sagittal (a) and transverse (b) views of a prostatic adenocarcinoma with marked mineralization. The distal acoustic shadowing artefacts, make imaging of the distal part of the prostate gland very difficult

attempt to diagnose cases of neoplasia. Within a large study trans-rectal three-dimensional power Doppler (3DPD) using CEUS was found to detect 68–79% of all tumour foci larger than 5 mm, leading the authors to conclude that 3DPD CEUS was the best single diagnostic tool for the detection of prostatic carcinoma (Unal et al. 2000). A recent study also noted that 3DPD CEUS had the potential to identify lesions where there was increased micro vessel density (Sedelaar et al. 2001), and Goossen et al. (2003) proposed that discrimination between left and right sided tumours could be accurately performed in 78% of cases using the same technique followed by off-line analysis. Most recently, Wink et al. (2008) documented good correlation between histological findings and CEUS in relation to tumour localization.

To our knowledge, this is the first study in veterinary medicine to describe the use of CEUS to evaluate prostatic perfusion in dogs with prostatic disease. The study used methods that were the same as those investigating normal prostatic perfusion (Russo et al. 2009), including a consistent anaesthetic protocol. The prostatic perfusion measurements for dogs with normal prostate glands in this study were similar to those previously reported by Russo et al. (2009). In this study, there were no significant differences between prostatic perfusion in dogs with benign prostatic pathology compared with the normal dogs. These findings probably relate to the fact that these pathologies are slow to develop and result in limited change in parenchymal histology at least over the course of several years. Subjective evaluation of the data showed differences amongst the tumours; in dogs with prostatic carcinoma, perfusion values were numerically higher than for normal dogs, whilst for the single dog with leiomyosarcoma, the perfusion was numerically lower than in normal dogs. Clearly, examination of a greater number of dogs is required to further elucidate these very preliminary observations. However, these general features are consistent with observations of similar tumours affecting other organ systems. For example, hepatic carcinomas demonstrate hyperperfusion during wash in, higher PPI than normal tissue, faster TTP and hypoechogenicity during the wash out phase (O'Brien et al. 2004) and are normally hypervascular, whereas no other lesions show hypervascularity (Kanemoto et al. 2009). Each of these features is similar to the four prostatic carcinomas described in this study. Furthermore, the leiomyosarcoma detected in this study has similar features to other sarcomas, such as hemangiosarcomas and undifferentiated sarcomas of the spleen, which are characterized in all phases by an homogeneous anechoic (non-perfused) area with surrounding highly vascularized parenchyma (peripheral irregular perfusion pattern) (Rossi et al. 2008; Haers and Saunders 2009).

In this study, dogs were also subjected to biopsy of the prostate gland, taken from random areas of the parenchyma unless there was an obvious focal lesion which was then targeted. There were no complications in any of the dogs following this procedure. It has been reported that further targeted biopsies during CEUS increase the detection rate of human prostate cancer. In dogs, random biopsies may still be a necessity, because targeted biopsies may miss cancers, especially when located in the transition zone. However, like in humans, the goal for future research should be improved visualization and localization of cancer to make random biopsies avoidable (Mitterberger et al. 2007). Contrast-enhanced ultrasound is a relatively non-invasive technique, which can be conducted more quickly and less expensively than a single biopsy. Biopsy and consequent histo-pathological examination are likely to be more sensitive methods for a definitive diagnosis, whilst for the moment data for CEUS is only available for the differentiation of benign from malignant conditions.

Although the results of this study are very encouraging, the technique did encounter some difficulty especially when there was marked parenchymal mineralization which impeded the visualization of the distal part of the prostate gland. Furthermore, when there was significant prostatomegaly it was not possible to display the entire prostate gland in a single field of view. Moreover, if the prostate was very large, there was a different brightness of the organ amongst the near and far field.

In conclusion, in this study, CEUS was superior to B-mode US for the diagnosis of prostatic disorders. Contrast-enhanced ultrasound showed features that may be promising for its use as a diagnostic tool in dogs with prostatic disorders, particularly for differentiating malignant from benign diseases. Whether CEUS should be used alone or in combination with other modalities needs further clinical investigation on a greater number of cases.

Conflicts of interest

None of the authors have any conflict of interest to declare.

Author contributions

All authors contributed equally to the work in this article.

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