International Journal of Impotence Research (2007) 19, 110–113
 0955-9930/07 $30.00
www.nature.com/ijir

CASE REPORT
Semiquantitative imaging measurement of baseline and vasomodulated normal prostatic blood flow using sildenafil

JR Haaga, A Exner, B Fei and AD Seftel

Department of Radiology, University Hospitals of Cleveland, Cleveland, OH, USA

The physiologic variability of blood flow to the prostate has not been studied until this time. We report the vasoactive effects of sildenafil and phenylephrine on blood flow of the normal prostate. Sildenafil increases prostate blood flow by approximately 75% and phenylephrine reduces the flow incrementally. Administration of these drugs with dynamic contrast-enhanced magnetic resonance imaging may improve the diagnosis of cancerous tissue because according to the literature, tumor angiogenic vessels lack the vasoactive physiologic response of the normal tissue.
International Journal of Impotence Research (2007) **19,** 110–113. doi:10.1038/sj.ijir.3901486; published online 25 May 2006

Keywords: prostate blood flow; vasoactive drugs; angiogenesis

Introduction

Blood flow of the normal prostate has received limited attention in the literature, except for establishment of a baseline comparison for the evaluation of inflammatory and cancerous processes. Although absolute quantitative methods for precise measurement of prostatic blood flow have yet to be developed, the most widely accepted method is the semiquantitative method, dynamic contrast-enhanced magnetic resonance imaging (DCE MRI).

DCE MRI of the prostate, as reported in the literature,[1] is performed by acquiring repeat MRI images over the prostate during the intravenous injection of gadolinium contrast material. The image data acquired over a local area of interest can be used to plot a curve of the signal intensity over time. Such curves semiquantitatively reflect the blood flow and vessel density in the area of interest (quantitative measurement is not possible because of the variable paramagnetic effects related to concentration variation).

Numerous authors have used this method to show differential enhancement between the normal gland and tumor.[2–6] The angiogenesis of prostatic cancer stimulates increased vessel growth and density (maximum vessel density) as compared to normal tissue.[1,2] Accordingly, DCE MRI of the tumor tissue demonstrates increased signal intensity reflecting the increased number of tumor blood vessels. The shortcoming of the current technique is the overlap of findings with prostatitis and cancer, because both can show increased signal intensity owing to increased blood flow.[2–6] A potential method of improving the differentiation of the two may be the use of vasoactive drugs that can induce characteristic changes in normal and tumor vessels.[7–10] Although not yet used in imaging, authors have shown in animal models that the vasodilators and vasoconstrictors cause the corresponding reaction in the normal vessels whereas tumor vessels do not react.

We herein present a case which demonstrates the vasoreactivity of normal prostate vessels produced by the type 5-phosphodiesterase (PDE5) inhibitor, sildenafil, a vasodilator, and the alpha vasoconstrictor pseudoephedrine. This vasomodulated change in blood measured on DCE MRI and may potentially form the basis for improved cancer imaging of the prostate. This is the first description of the effects of these drugs on prostate blood flow.

Case history

A 59-year-old white male with no history of prostate cancer and normal prostate-specific antigen, volunteered for multiple DCE MRI examinations of the prostate to evaluate vasoactive modulation of the normal blood flow. Three separate examinations were

Correspondence: Dr J Haaga, Department of Radiology, University Hospitals of Cleveland, 11100 Euclid Avenue, Cleveland, OH 44106, USA.
E-mail: Haaga@UHRAD.com
Received 28 October 2005; revised 8 March 2006; accepted 6 April 2006; published online 25 May 2006

performed several weeks apart. The studies were performed on a Siemens 1.5 T Symphony scanner. The DCE MRI examination included Siemens's tfiperf (inversion fisp) sequence. TR = 3000, TE = 1.27, TI = 400, flip angle = 50°. Gadolinium versetamide 33.9 mg, injection at 2 cc/s for a total of 20 cc. Images were obtained every 3 s for a total period of 5 min and every minute thereafter for 15 min.

All three studies were performed with identical MRI sequences and parameters. The first study was performed without a vasoactive drug but the second and third studies were repeated with administration of a vasoactive drug, sildenafil or pseudoephedrine. The second DCE MRI study was performed 1 week later, and the gadolinium injection was performed after the oral ingestion of 25 mg of sildenafil 1 h before the study. The third DCE MRI was performed identical to the second study with the oral administration of 25 mg of sildenafil 1 h before the study, and the administration of 60 mg of pseudoephedrine 20 min preceding the gadolinium injection. The absorption rate of each drug is quite predictable according to the literature, so the initial part of the study performed before the pseudoephedrine was administered, and the subsequent study had a vasodilator combined with a vasoconstrictor.

Data analysis was performed using ANALYZE data management software (Analyze Direct, Inc., Lenexa, KS, USA) and Excel (Microsoft, Seattle, WA, USA). Data graphs were normalized to the blood flow of the iliac artery. The data were acquired during the 5-min period following intravenous gadolinium injection and thereby provide a semi-quantitative assessment of blood flow characteristics (see Discussion).

The results of the intensity curves are seen in Figure 1a–c. Clinical MRI images showing enhancement after sildenafil are noted in Figure 2a–c. Comparing the baseline intensity flow curve with the sildenafil curve (Figure 1a and b), several observations can be made. The enhancements of the lateral and central portions of the prostate on the two studies begins at 21 s and show significant differences in the amount of total enhancement and relative enhancement between the two lobes. Most importantly, comparing the baseline enhancement curve (without sildenafil) to the vasodilatory enhancement curve with sildenafil, there is more

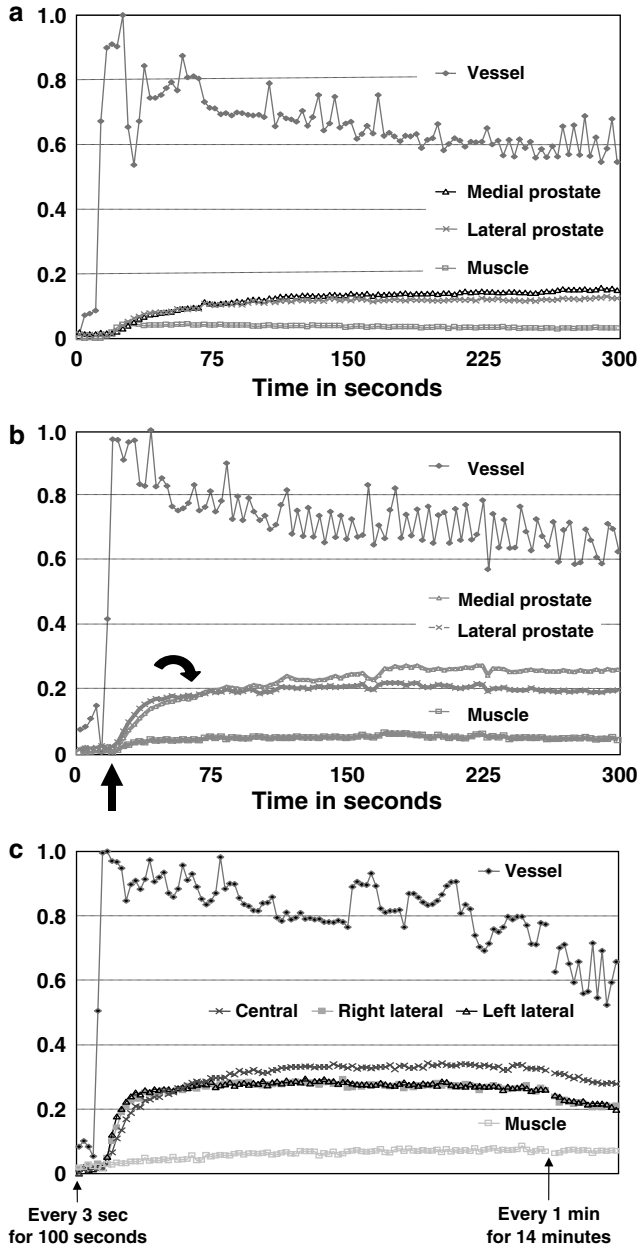

Figure 1 (**a**) Gadolinium enhancement after bolus injection of 20 cc of gadolinium versetamide without sildenafil dosage. Intensity time curve plots intensity value against time in seconds over prostate medial and lateral lobe, normalized to adjacent internal obturator muscle, and femoral artery. In the early vascular phase, the enhancement of the lobes is quite gradual and maximizes after minutes. At this time, the intensity includes both the vascular and extra-vascular space. Note the increased enhancement of the medial lobe above the lateral lobe. (**b**) Sildenafil study with gadolinium enhancement after bolus of 20 cc of gadolinium and versetamide 30 min after sildenafil. The same pulsing sequence and time intervals were used on the second examination as the one displayed in (**a**). The enhancement uptake in the early vascular phase is much more rapid with the vasodilator and the maximum enhancement is 73% greater in the lateral lobe than the enhanced, undilated study above. The medial lobe after sildenafil (Viagra) enhances 78% greater than the medial lobe of the enhanced undilated study. Note also there is greater vascular enhancement of the lateral lobe than the medial lobe beginning at 21 s after the bolus, arrow. At 72 s, curved arrow, the medial lobe enhancement increases to exceed that of the lateral lobe. (**c**) Sildenafil and pseudoephedrine study. Patient had oral dose of sildenafil 25 mg, 1 h before study and oral dose of pseudoephedrine 60 mg before injection of gadolinium contrast (20 cc of versetamide). Early part of curve shows similar overall enhancement and separation of medial and lateral lobe enhancement as noted in (**b**). Also note that in the equilibration phase at 14 min when pseudoephedrine serum levels are increasing, there is a definite decrease in intensity owing to vasoconstriction. Gastrointestinal absorption kinetics is well defined over time and is unaffected by food, drink or any other parameters.[16]

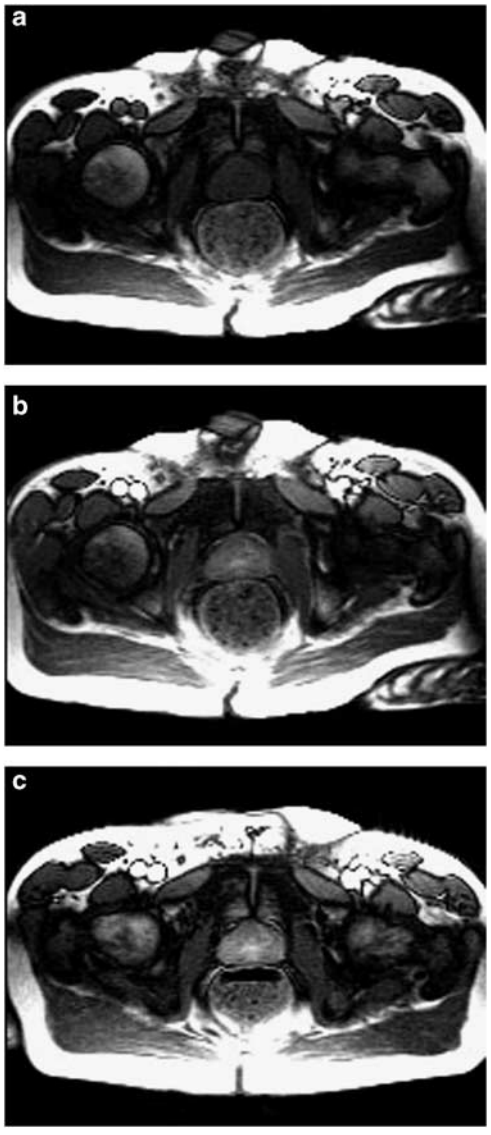

Figure 2 (**a**) MRI image of the prostate as baseline before the injection of gadolinium. Note the almost equivalent intensity of the obturator, muscle and prostate. (**b**) MRI image of the prostate at maximum enhancement after gadolinium injection. No sildenafil was given during this study. (**c**) MRI image of separate MRI study on different day after a dose of sildenafil 50 mg, and injection of gadolinium. Note greater enhancement of the gland than in (**b**), and note the graphic analysis in Figure 1a and b.

than 70% increase throughout the entire scan period of 5 min (300 s). Also of great interest is the differential enhancement seen on the comparison studies of the medial and lateral lobes during the early phase and later phase of contrast. Between 21 and 72 s, the medial lobe increased by 73% and the lateral lobe increased by 78% on the sildenafil study compared to the baseline study. On the baseline study without sildenafil, there was essentially no difference in the enhancement between the medial and lateral lobes during the early phase. Comparing the baseline scans and the sildenafil enhanced scan after 72 s shows increased enhancement of the medial lobe compared to the lateral lobes but to a greater degree than on the baseline.

The DCE MRI study with sildenafil and pseudoephedrine is equally interesting. Firstly, the enhancement pattern of the medial and lateral lobes of the prostate are again demonstrated during the early phase of the study. Most interesting are the changes in blood flow, which occur in the later phases. After 14 min, there was a reduction of about 20% in the enhancement. At this phase of the gadolinium equilibrium, the intensity depends upon the intravascular and extravascular concentration. Because the diffusion to the extravascular space would not be affected, the reduction in intensity must be secondary to vascular constriction in the gland.

Discussion

Our discovery of the vasoactive effects of sildenafil and pseudoephedrine on normal prostate vessels and the ability to semiquantify those changes during DCE MRI scanning has two significant implications. Firstly, it demonstrates that the vascular receptor sites for sildenafil (PDE5 inhibitor) and the alpha sites for pseudoephedrine are present in the prostate vessels as well as in the penis. Secondly, the vasodilatation and increased enhancement of the normal prostate vessels detectable by DCE MRI has the potential for improved diagnosis of prostatic cancer and inflammation.

Whereas Medina *et al.*[11] among others have confirmed the effect of PDE5 inhibitors, such as sildenafil, to produce vasodilation and pseudoephedrine to produce vasoconstriction[12] of the penile arterioles, the effect on the prostate has not been previously documented. We anticipated this observation owing to the recent findings of the PDE5 in the prostate,[13] whereas alpha-adrenregic receptors exist in the prostate as well.[14] In cases of priaprism induced by these inhibitors, the oral administration of pseudoephedrine has been used to reduce blood flow by constriction of penile vessels to alleviate the erection.[15]

This confirmation of the vasoreactivity of normal prostate vessels provides the basis for exploiting the reported structural and functional differences of normal and prostate tumor vessels. Although normal vessels have smooth muscle pericytes that are reactive, tumor vessels lack such cells. Using quantitative immunohistochemical staining (CD34 endothelial cells and alpha smooth muscle antibody for mural cells) of human prostate tumor, Eberhard *et al.*[16] noted that prostatic tumor vessel pericytes were lacking in 70% of vessels. Additional rationale to expect non-reactivity from tumor vessels was noted by Mattson *et al.*[7,8] who said that even if occasional pericytes are present in tumor vessels, the low pH produced by the hypermetabolism produces maximal local vasodilatation.

The paradoxical indirect effect of normal vessel vasoactive response on tumor blood flow was demonstrated by Zlotecki *et al.*[10] and Hori *et al.*[9] Their animal model data demonstrated that when normal vessels react by dilating or constricting, the opposite effect is paradoxically induced in tumor vessels. When normal vessels dilate, the blood is 'pulled' away from tumor vessels producing a 'steal' phenomenon. When normal vessels constrict, the blood is 'pushed' to the tumor vessels increasing their relative blood flow. The possibility of using this principle during dynamic imaging was reported by Haaga[17] at a recent symposium. He reported that in several clinical human cases, they observed a similar paradoxical 'steal' of blood flow from tumor to normal cells, in liver and kidney cancer, on DCE MRI imaging. This effect was demonstrated by comparing signal intensity/time curves on baseline and vasodilator-modulated studies.

The need for an improved method of DCE MRI is apparent from the inconsistent results reported in the literature. Sommer *et al.*[2] found that prostatitis and cancer were enhanced in a similar fashion, but subsequent authors showed differential signal measurement between the two during peak enhancement phase. On the other hand, Preziosi *et al.*[3] showed significant differences for prostate cancer in mean tumor maximal enhancement, mean tumor rise time and greatest washout slope versus normal prostate. The nonspecificity was emphasized by Nowlrowski *et al.*,[4] who reported that maximal intensity enhancement and fastest peak occurs with stromal hyperplasia exceeding that of even cancer. Padhani *et al.*[5] showed no peak enhancement differences, permeability or leakage modeling parameters between the medial zone and cancer. With central gland tumors comprising 30% of malignancies, he concluded that it is quite difficult to detect such cancers with MRI alone.

With the demonstrated vasoreactivity of normal prostate vessels, we propose developing a DCE MRI examination, which exploits the vasomodulation differences between normal and cancer vessels. To this end, sildenafil and pseudoephedrine either as single or combined (temporal differences of administration) would be well suited because of their overall high safety margin. Sildenafil's low incidence of side effects as a treatment for erectile dysfunction is well known and it appears to not adversely affect tumor growth. Qian *et al.*[18] reported that sildenafil did not promote tumor cell growth in an orthotopic prostate cancer model, so any concern about promoting tumor growth is minimal.

To our knowledge, this is the first report of increased enhancement and blood flow of the normal prostate, produced by a PDE5 inhibitor, sildenafil and decreased enhancement induced by pseudoephedrine. Because of the vasoreactivity of the normal prostate vessels to such agents, we believe vasoactive drugs may form the basis for a new imaging approach to differentiate cancer from normal and inflammatory tissues.

Acknowledgments

We thank Jack Jesberger for reviewing the technical aspects of the MRI data.

References

1 Buckley DL, Roberts C, Parker GJ, Logue JP, Hutchinson CE. Prostate cancer: evaluation of vascular characteristics with dynamic contrast-enhanced T1-weighted MR imaging – initial experience. *Radiology* 2004; **233**: 709–715.
2 Sommer FG, Nghiem HV, Herfkens R, McNeal J. Gadolinium-enhanced MRI of the abnormal prostate. *Magn Reson Imaging* 1993; **11**: 941–948.
3 Preziosi P, Orlacchio A, Di Giambattista G, Di Renzi P, Bortolotti L, Fabiano A, Cruciani E, Pasqualetti P. Enhancement patterns of prostate cancer in dynamic MRI. *Eur Radiol* 2003; **13**: 925–930.
4 Noworolski SM, Henry RG, Vigneron DB, Kurhanewicz J. Dynamic contrast-enhanced MRI in normal and abnormal prostate tissues as defined by biopsy, MRI, and 3D MRSI. *Magn Reson Med* 2005; **53**: 249–255.
5 Padhani AR, Gapinski CJ, MacVicar DA, Parker GJ, Suckling J, Revell PB *et al.* Dynamic contrast enhanced MRI of prostate cancer: correlation with morphology and tumour stage, histological grade and PSA. *Clin Radiol* 2000; **55**: 99–109.
6 Oyen RH. Dynamic contrast-enhanced MRI of the prostate: is this the way to proceed for characterization of prostatic carcinoma? *Eur Radiol* 2003; **13**: 921–924.
7 Mattsson J, Lilja J, Peterson HI. Influence of vasoactive drugs on local tumor blood flow. *Eur J Cancer Clin Oncol* 1982; **18**: 677–684.
8 Mattson J, Appelgren L, Karlsson L, Peterson HI. Influence of vasoactive drugs and ischaemia on intra-tumour blood flow distribution. *Eur J Cancer* 1978; **14**: 761–764.
9 Hori K, Zhang QH, Saito S, Tanda S, Li HC, Suzuki M. Microvasculare mechanisms of change in tumor blood flow due to aniotensin II, epinephrine and methoxamine: a functional morphometric study. *Cancer Res* 1993; **53**: 5528–5534.
10 Zlotecki RA, Baxter LT, Boucher Y, Jain RK. Pharmacologic modification of tumor blood flow and interstitial fluid pressure in a human tumor xenograft: network analysis and mechanistic interpretation. *Microvasc Res* 1995; **50**: 429–443.
11 Medina P, Segarra G, Vila J, Domenech C, Martinez-Leon JB, Lluch S *et al.* Effects of sildenafil on human penile blood vessels. *Urology* 2000; **56**: 539–543.
12 Lowe FC, Jarow JP. Placebo-controlled study of oral terbutaline and pseudoephedrine in management of prostaglandin E1-induced prolonged erections. *Urology* 1993; **42**: 51–53.
13 Uckert S, Oelke M, Stief CG, Andersson KE, Jonas U, Hedlund P. Immunohistochemical distribution of cAMP- and cGMP-phosphodiesterase (PDE)isoenzymes in the human prostate. *Eur Urol* 2006; Jan 18 [E-pub ahead of print].
14 Preston A, Frydenberg M, Haynes JM. A1 and A2A adenosine receptor modulation of alpha 1-adrenoceptor-mediated contractility in human cultured prostatic stromal cells. *Br J Pharmacol* 2004; **141**: 302–310.
15 Sadeghi-Nejad H, Dogra V, Seftel AD, Mohamed MA. Priapism. *Radiol Clin North Am* 2004; **42**: 427–443.
16 Eberhard A, Kahlert S, Goede V, Bernhard H, Hemmerlein B, Plate KH *et al.* Heterogeneity of angiogenesis and blood vessel maturation in human tumors: implications for antiangiogenic tumor therapies. *Cancer Res* 2000; **60**: 1388–1393.
17 Haaga J. Interventional CT: 30 years experience. *Eur Radiol* 2005; **15**: D116–D120.
18 Qian C, Takahashi M, Kahnoski RJ, Teh BT. Effect of sildenafil citrate on an orthotopic prostate cancer growth and metastasis model. *J Urol* 2003; **170**: 994–997.

Haaga JR, Exner A, Fei BW, Seftel A. Semiquantitative imaging measurement of baseline and vasomodulated normal prostatic blood flow using sildenafil. International Journal of Impotence Research 2007;19:110-3.