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Wideband harmonic imaging: A novel contrast ultrasound imaging technique

A. Bauer[1], **P. Hauff**[1], **J. Lazenby**[2], **P. von Behren**[2], **M. Zomack**[1], **M. Reinhardt**[1], **R. Schlief**[1]

[1] Schering AG, Clinical Development Diagnostics, D-13342 Berlin, Germany
[2] Siemens Medical Systems, Issaquah, WA, USA

Abstract. A novel ultrasonic imaging method, wideband harmonic imaging, for nonlinear imaging of microbubble contrast agents is evaluated. In wideband harmonic mode, two pulses of alternate phase are send out. The image is then processed from the sum of both pulses, resulting in an image of nonlinear scatterers such as microbubbles. A prototype ultrasound system, Siemens Elegra, was evaluated with in vitro investigations and animal trials, using conventional, harmonic and wideband harmonic settings with the galactose based ultrasound contrast agent Levovist. Wideband harmonic imaging offers superior sensitivity for ultrasound contrast agents compared to conventional imaging and harmonic imaging. At low transmit power settings (MI 0.1–0.5) the nonlinear response is already sufficient to generate a image of the blood pool distribution of Levovist in the rabbit kidney including the microvasculature, with clear delineation of vessels and perfused parenchyma. At high transmit amplitudes, nonlinear tissue response reduced the apparent image contrast between contrast agent and tissue. The results suggest that wideband harmonic imaging is currently the most sensitive contrast imaging technique, maintaining highest spatial resolution. This may add to image quality and offer new clinical potential for the use of ultrasound contrast agents such as Levovist.

Introduction

Recent experience with Levovist (Schering, Berlin, Germany) has shown that diagnostic applications may go far beyond echo enhancement for previously failed Doppler examinations. Imaging the active bubble response of Levovist is facilitated with novel approaches to ultrasonic imaging such as wideband harmonic imaging, and opens up new diagnostic opportunities.

Currently, the diagnostic usage of microbubbles is focusing mainly on the application for Doppler enhancement. This allows the performance of Doppler examinations in patients who are difficult to scan or in problematic areas such as renal arteries and transcranial examinations. However, the nonlinear properties of microbubbles allow a different approach for imaging: Since tissue responds mostly linear to incident ultrasound and microbubbles are mostly nonlinear, these properties can be used for a subtraction technique, similar to digital subtraction angiography, the so-called harmonic imaging. The systems can be tuned to the second harmonic frequency by the use of a broadband transducer and subsequent filtering of the signal at the double of the transmit frequency [1]. Such systems have a sensitivity advantage and significantly reduced clutter for Doppler applications [2]. The disadvantage of such an system is, however, that a large portion of the nonlinear signals from microbubbles is filtered out and therefore not used.

The nonlinear properties of microbubbles were first described by Lord Rayleigh [3] long before their use as ultrasound contrast agents was envisaged. Recent studies of the underlying properties of microbubbles have contributed to a better theoretical understanding of the microbubble in an ultrasound field [4] and the active behavior of such a microbubble [5]. This active behavior, stimulated acoustic emission, is also used for other applications, such as late-phase imaging of liver lesions with conventional Color Doppler instruments [6, 7].

To exploit the nonlinear properties of ultrasound contrast agents in an optimized fashion, a technique using alternate phasing was suggested [8]. Ideally, with the summation of two alternately phased pulses, any linear scatterer, such as tissue, should be canceled out. Any nonlinear echo that is in the frequency range of the transducer should be detected in its entire intensity. Consequently, any nonlinear scatterer, such as a microbubble, is imaged with optimum sensitivity. The limitations of tissue to microbubble contrast should only be due to nonlinear propagation in tissue, which creates a small nonlinear signal [9]. Wideband harmonic imaging

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Correspondence to: A. Bauer

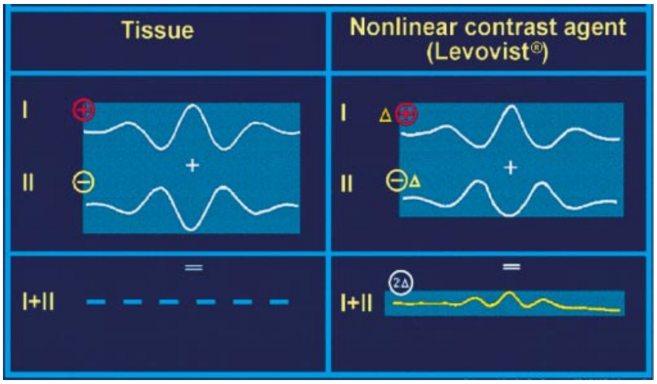

Fig. 1. Signal processing in wideband harmonic: Two pulses are sent out with opposite phase (phase inversion). The sum of both pulses is displayed in the image: for tissue the resulting summation results in a cancellation of the two pulses. For nonlinear contrast agents all nonlinear echoes are added up and a signal is generated, since compression and expansion is not

is therefore an extension of the harmonic imaging techniques used thus far. Depending on nonlinear response from microbubbles, this mode is designed to utilize the full bandwidth of the ultrasound system on the receive side. The first animal studies of this technique indicated a potential of wideband harmonic imaging [10]. This study uses this technology in a clinical prototype scanner to evaluate diagnostic potential with the use of ultrasound contrast agents.

Materials and methods

For the studies an experimental ultrasound system (Elegra, Siemens Medical Systems Inc., Issaquah, Wash.) was used, with second harmonic and wideband harmonic imaging within the same equipment. For both modes, color and B-mode display of the harmonic and wideband harmonic image were selected. All normal functions of the system, such as conventional color Doppler, were available as well.

The processing of the wideband harmonic follows the schematic drawing of Fig. 1: Two pulses are sent out with opposite phase (phase inversion); for tissue the resulting summation results in a cancellation of the two pulses. For nonlinear contrast agents all nonlinear echoes are added up and a signal is generated. The main reason for the nonlinear response of microbubbles is the difference of expansion and compression phase with a higher resistance for the compression, and the generation of harmonics due to resonance phenomena.

The galactose-based echo enhancer Levovist (Schering, Berlin, Germany) was used in this study, to date the only ultrasound contrast agent approved for clinical use in radiological applications. Levovist was used in 300 and 400 mg/ml concentrations and was applied via an injection system (Pulsar, Medrad, Pittsburgh, Pa.) for accurate delivery of the contrast agent. The nonlinear properties of Levovist allow imaging in harmonic B-mode and Doppler applications. Levovist has very prominent nonlinear properties, and is applied for harmonic imaging as well as other nonlinear techniques [6].

In vitro experiments were performed in a water tank with a dialysis tubing to adjust the principal imaging parameters for Levovist. The flow in the dialysis tube can be adjusted from zero to approximately 50 cm/s, Levovist is injected at a speed of 1 ml/min. The experiments were mainly to optimize settings under standardized conditions.

The optimized settings were subsequently investigated in two beagle dogs and three New Zealand rabbits. For both models, the liver and the kidney were imaged in second harmonic and wideband harmonic mode as well as in conventional Doppler mode. A 3.5-MHz curved array was used in all experiments.

Results

From the in vitro experiments the optimum settings for imaging with second harmonic and wideband harmonic power mode were investigated. The transmit amplitude was varied between 1 and 100 % of the maximum. For

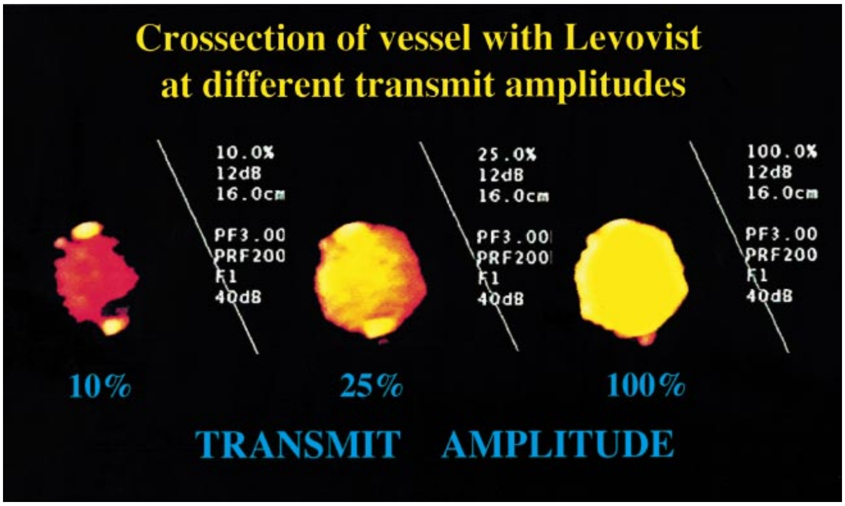

Fig. 2. Increase of transmit amplitude. The experiment shows a cross section of a dialysis tube with Levovist (Schering, Berlin, Germany) at the same concentration. As the transmit amplitude is increased, more nonlinear signals from the contrast agent are detected, resulting in a brighter and more homogeneous signal from inside the dialysis tubing. The highest signal intensity is achieved with the highest transmit amplitude. Since at this amplitude destruction of microbubbles is present, it can be inferred that destruction during one pulse pair adds significantly to the signal yield of wideband harmonic

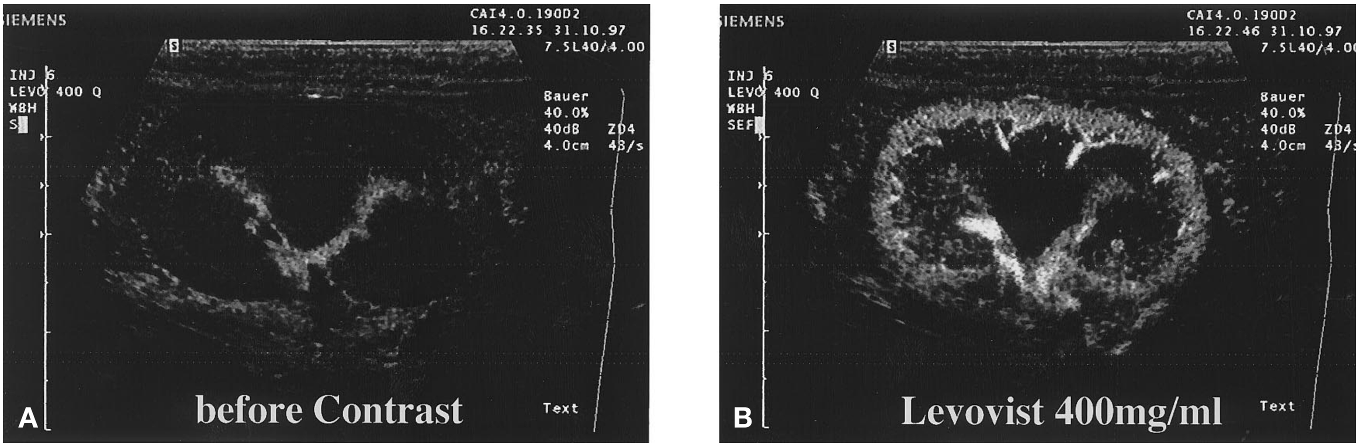

Fig. 3. Beagle kidney before and after Levovist in wideband harmonic mode: In the precontrast image nonlinear tissue response enables delineation of the kidney. The contrast enhanced study shows a complete image of the vascular compartment of the kidney, including microvessels, in a homogeneous and clear way. The resolution is at the level of the conventional B-mode, resulting in a clear and easy to interpret image of the kidney vascularization

Table 1. Transmit power level vs received signal intensity (relative units)

Transmit (%)	Wideband harmonic	Second harmonic
1	0.09	0.02
10	0.31	0.04
25	0.62	0.26
100	1.00	0.56

both, second harmonic (2.5-MHz transmit, 5-MHz receive) and wideband harmonic settings (2.5-MHz transmit, full receive bandwidth), the highest transmit amplitude (100%) was favorable, resulting in the highest signal intensity in the image. Figure 2 delineates the improved signal intensity with a higher transmit amplitude.

The comparison between the signal intensity of the harmonic mode and the wideband harmonic mode showed a higher signal yield in wideband harmonic mode for all transmit amplitudes (1, 10, 25, 100), with the maximum difference at 10% amplitude.

In the beagle dogs, the contrast effect after Levovist injection was visible in all injections using wideband harmonic. Delineation of the contrast-filled areas (parenchyma vs gallbladder or urinary system) was clearly possible in all injections given. The sensitivity for Levovist could be improved by triggered imaging. With medium transmit amplitude (MI 0.1–0.5), the contrast-filled areas were only incompletely visualized in second harmonic mode. With wideband harmonic at medium transmit amplitudes clear delineation of vessels and perfused parenchyma with almost no signals present at baseline was achieved. Figure 3 shows a pre- and postcontrast image of a beagle kidney. Whereas in the precontrast image the outline of the kidney is visualized clearly (due to nonlinear tissue response), the contrast-enhanced image shows a complete image of the vascular compartment of the kidney, including microvessels, in a homogeneous and clear way. The resolution is at the level of the conventional B-mode, resulting in a clear and easy way to interpret image of the kidney vascularization.

At highest transmit amplitude, the nonlinear response of tissue was apparently visualized in wideband harmonic mode in addition to contrast-filled areas. This effect was less prominent in second harmonic mode.

Discussion

Wideband harmonic imaging with Levovist is feasible and may be an improvement over conventional and second harmonic imaging. This is especially important for low transmit power settings, which may enable a improved imaging even in problem areas with attenuation.

At low transmit amplitude the improvement over second harmonic imaging is most marked in vitro, and a complete delineation of vascular and microvascular compartments in vivo was possible. It is therefore expected to be the optimum setting for human applications as well; however, due to scaling factors, a slightly raised transmit amplitude may be necessary. With these results there seem to be few limitations for the application of this technique in humans.

At highest transmit amplitudes, nonlinear tissue response reduced the apparent image contrast between contrast agent and tissue, since nonlinear tissue effects are present, interfering with contrast agent visualization. Additionally, for high-transmit amplitudes during the course of the insonation the bubble is destabilized and loses its gaseous content [11]. This effect, destruction of contrast microbubbles, reduces the number of microbubbles in the image and therefore reduces the contrast. This effect can be compensated by triggered imaging, [12] but at the expense of the real-time analysis.

Wideband harmonic imaging is a significant improvement for ultrasonic contrast imaging. Its promising potential should be further evaluated in clinical studies to exploit the improved sensitivity with a very good spatial resolution. The further adaptation of ultrasonic equipment to contrast-enhanced scanning and the utilization of nonlinear microbubble properties is expected to impact the future diagnostic opportunities with contrast ultrasound.

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