THE FIFTH HEART CENTRE EUROPEAN
SYMPOSIUM ON ULTRASOUND CONTRAST IMAGING

ABSTRACTBOOK

The Fifth Heart Centre Symposium on Ultrasound Contrast Imaging

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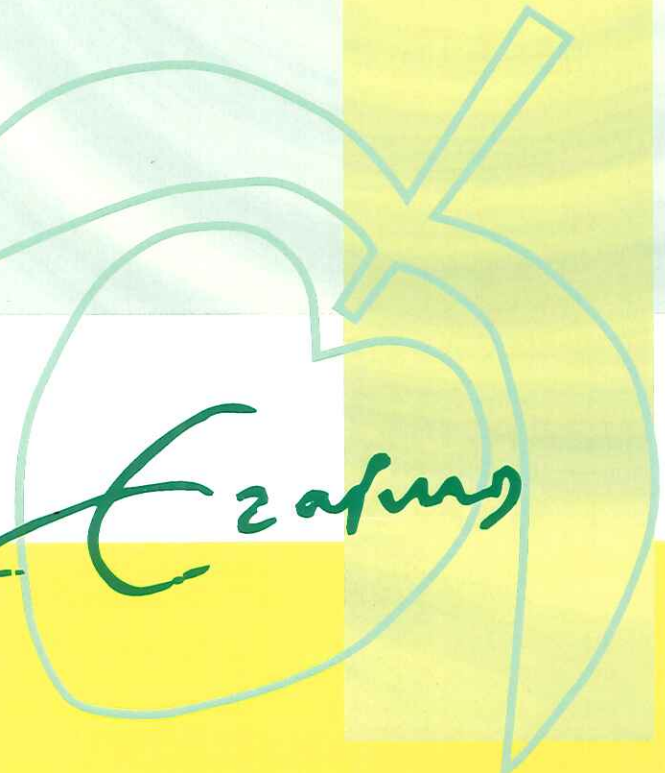

Nycomed Amersham

ICIN

to be held on *January 20 - 21, 2000*
Rotterdam The Netherlands

5th HEART CENTRE EUROPEAN SYMPOSIUM ON ULTRASOUND CONTRAST IMAGING.
19 - 21 JANUARY 2000, Rotterdam, The Netherlands.

WEDNESDAY **19 January 2000**

15.45 **Thesis Defence by Peter Frinking** ..... **Erasmus Medical School**

18.00 - 20.00 **Registration - Welcome Drinks - Posters** ..... **Inntel Hotel**

THURSDAY **20 January 2000**

08.00 - 09.00 **Registration**

09.00 Opening address by N. Bom

09.05 - 10.35 **CARDIAC AND OTHER APPLICATIONS** ..... *Chairperson: P. Nihoyannopoulos*

M.J. Monaghan — Optimal myocardial perfusion imaging: when and where, greyscale harmonics, powerdoppler or pulsed inversion? 1

H. Becher — Clinical value of myocardial perfusion imaging using Power Doppler 4

J. Østensen — Myocardial perfusion imaging - Problems to solve and need for standardization 5

L. Agati — Assessment of no-reflow phenomenon after acute myocardial infarction using harmonic power Doppler and intravenous pump infusion of Levovist®: comparison with intracoronary contrast injection 7

Discussion — *Do we need nuclear myocardial perfusion imaging in the 21st century?*

10.35 - 11.00 **Intermission**

11.00 - 12.30 **TECHNOLOGY I** ..... *Chairpersons: H. Torp and M.J. Monaghan*

P. Burns — The effect of bubble depletion on destruction–reperfusion flow measurement with contrast 8

M. Averkiou — Real time perfusion imaging with ultrasound contrast agents 9

N. de Jong — Design of a phased array transducer for contrast imaging 13

K. Ferrara — Optical visualization of bubbles in an ultrasound field 16

Discussion — *What is needed for further improvements: new agents or new technologies?*

12.30 – 14.00 Lunch

14.00 - 15.45 **RADIOLOGY** ..... *Chairpersons: D.O. Cosgrove and F. Moriyasu*

F. Moriyasu — Vascular and parenchymal enhancement of the liver with a novel contrast agent 17

D.O. Cosgrove — Functional haemodynamic studies in renal transplants 19

T. Albrecht — Up-date on late phase imaging in the liver: preliminary results of a multicenter trial 21

J.M. Correas — Functional imaging of renal transplants using contrast-enhanced sonography with triggered pulse inversion imaging: results of a pilot study 23

M. Lange — New perspectives in brain perfusion imaging 24

Discussion — *Why do we need ultrasound contrast in radiology?*

15.45 – 16.15 **Intermission**

16.15 – 17.45 **YOUNG INVESTIGATOR AWARD** ..... *Chairperson: P. Burns*

Y. Kono — The mechanism of parenchymal enhancement of the liver by microbubble-based ultrasound contrast agent: an intravital microscopy study 25

A. Kopitzko — Low contrast dose reflux - Sonography in children with phase inversion imaging 27

K. Kuribayashi — Observation of the behavior of microbubbles exposed to ultrasound using a high-speed camera 29

S. Schettler — Improved sonographic detection of liver metastases with contrast enhanced wideband harmonic imaging 33

W. Wilkening — Brain perfusion imaging using contrast agent specific imaging modes 34

19.00 - 22.30 **SOCIAL EVENT "Bubbles on the river" (incl. Dinner)** 75

5th HEART CENTRE EUROPEAN SYMPOSIUM ON ULTRASOUND CONTRAST IMAGING.
19 - 21 JANUARY 2000, Rotterdam, The Netherlands.

FRIDAY **21 January 2000**

07.30 - 08.00 **Registration**

07.30 - 09.00 **POSTER DISCUSSION** *Moderators: F.J. ten Cate and N. de Jong*

09.00 - 10.30 **TECHNOLOGY II** *Chairpersons: D. Lohse and N. de Jong*

Discussion — *How can the ultrasound companies contribute to the improvement of contrast imaging?*

10.30 - 11.00 **Intermission and ROTTERDAM-YIA**

11.00 - 12.30 **FUTURE DIRECTIONS** *Chairpersons: S. Feinstein and T. Porter*

Discussion — *What more can we do with ultrasound contrast bubbles?*

12.30 - 13.45 **Lunch**

13.45- 15.00 **CLINICAL CASES** *Chairperson: F.J. ten Cate*

15.00 - 15.30 **DISCUSSION AND CONCLUSIONS** *F.J. Ten Cate and N. de Jong*

15.30 **Adjourn**

First Announcement 2001

OPTIMAL MYOCARDIAL PERFUSION IMAGING: WHEN AND WHERE, GREYSCALE HARMONICS, POWER DOPPLER OR PULSE INVERSION?

Mark J. Monaghan

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As contrast echocardiography enters a new millennium, the question is no longer can we visualise myocardial perfusion but can we do it reproducibly, reliably, in all myocardial segments and in a variety of clinical settings? In order to tackle those remaining challenges we need to consider which contrast imaging technology is likely to work best with which type of contrast agent and in which clinical scenario. Unfortunately, our answers to those questions are not complete however we can apply some basic principles to examine the interaction between different types of imaging modalities and different contrast agents which may provide some pointers for the future.

Harmonic power Doppler is an imaging technique, which relies on bubble destruction within the myocardium. This bubble destruction causes a loss of correlation between sequential imaging pulses which can be interpreted by the imaging system to represent the presence of contrast microspheres. When power Doppler is used to study blood flow in vessels or cavities, loss of correlation is caused by moving red blood cells. In the myocardial microvasculature blood cell velocities are too low to cause loss of correlation and this occurs, as previously mentioned, because of bubble destruction. Therefore, the ideal contrast agent to use with this type of imaging would contain microbubbles which are strong enough to persist until they reach the myocardium. However, within the myocardium the bubble then needs to be destroyed. This requires high power which in itself can induce a high tissue signal, although this can usually be filtered out. Ideally, the microbubble gas should be air, so that it dissolves rapidly once the shell is broken. However, air requires a tough, thick bubble shell to prevent it leaking out before the myocardium is reached. A tough, thick bubble shell is likely to be resistant to destruction, in theory making this less suitable for harmonic power Doppler. One possible solution to this apparent paradox would be to use an initial high energy destruction pulse, which can be filtered out of the imaging bandwidth, and then to study decorrelation caused by dissolution of released gas using further low energy pulses.

Using available 2nd generation ultrasound agents harmonic power Doppler does appear to be sensitive for the detection of myocardial perfusion and it has the significant advantage of being easy to visually appreciate. This latter attribute has made it popular with investigators. However, there are a number of disadvantages, which limit its application. These include the fact that the technique must be used with intermittent imaging, it has less dynamic range than other technologies, pseudo perfusion defect

artefacts can occur (lateral wall and apex) and wall motion artefacts can create the appearance of perfusion where non might exist.

The other contrast imaging technologies can mainly considered to be non-destructive methods and rely on the non-linear response of contrast microbubbles to ultrasound. Greyscale harmonic imaging utilises the fact that contrast microbubbles may resonate in an ultrasound field of sufficient energy. As the microbubbles resonate they generate harmonics of the transmitted fundamental signal. Separation of the harmonic signal from the fundamental is performed by bandpass filtering within the receive circuitry. However, tissue harmonics are also generated and it is important that these not so high in amplitude that they mask the contrast harmonic signal. Therefore, the trade-off here is to ensure that the power of the transmitted signal is sufficient to create microbubble harmonics, without extensive bubble destruction and generation of large tissue harmonics.

Pulse inversion imaging utilises two sequential pulses 180^0 out of phase with each other. The non-linear bubble response to each pulse is different, depending on the pulse phase. When the received echoes from the two pulses are summed within the receiver circuitry the signals from linear scatterers/reflectors cancel each other out, whereas the non linear bubble response creates a signal which is effectively the harmonic. So pulse inversion imaging is essentially another method of detecting bubble harmonics without using filtering. This means that the ultrasound signal can effectively be of a broader bandwidth, which improves spatial resolution. For certain contrast agents, pulse inversion imaging appears to be very sensitive, however it is usually a grey scale display which needs some form of post processing (as does conventional harmonic imaging). In addition, some bubble destruction does occur with both methods which means that intermittent imaging is usually required. Accelerated intermittent imaging utilises low output power to limit bubble destruction and therefore the imaging frame rate can be increased to allow some evaluation of wall motion and thickening alongside perfusion. This is obviously not possible with conventional intermittent imaging and is likely to be of value during stress perfusion studies. The ideal bubble for both grey scale harmonic and pulse inversion imaging methods would be one which is flexible and able to resonate, therefore it is likely to require a soft shell but one which is also resistant to breakage.

Improvements to the methods described here will include power pulse inversion imaging which is effectively a combination of power Doppler and pulse inversion imaging. Early results show high sensitivity at low output power which means that perfusion can be studied in real-time, again this would permit simultaneous evaluation of wall motion and perfusion. This methodology would also allow evaluation of reflow kinetics, following bubble destruction, as a method of quantifying perfusion. A high energy pulse is delivered to destroy bubbles within the myocardium, and then the reflow of contrast is analysed using continuous power pulse inversion imaging. Ideally, a very stable persistent contrast microbubble would be required, however it should have a critical fragility, allowing

it to be destroyed by the high-energy pulse. This methodology may also allow evaluation of the cyclic variation of contrast intensity between systole and diastole and it is hoped that this may be yet another method of evaluating myocardial blood flow in the near future. New transducer technology, especially utilising lower frequencies may also soon be available. Lower frequencies may provoke a greater non-linear microbubble response, provide greater penetration at lower output power and reduce contrast attenuation.

The optimal method for myocardial perfusion imaging using echo contrast has not yet been fully developed and it is still some way from being evaluated in different clinical settings. Nevertheless progress in this field is now rapid and with the imminent release of new agents and imaging technologies, it is likely that the answers to the questions posed at the beginning of this abstract will soon be found.

CLINICAL VALUE OF MYOCARDIAL PERFUSION IMAGING USING POWER DOPPLER

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University of Bonn, Germany

Harmonic Power Doppler takes advantage from dissolution of microbubbles.
There have been numerous efforts to increase the stability of the microbubbles, another approach to deal with bubble instability is to enhance dissolution of microbubbles and take advantage of the loss of correlation (LOC) which orginate from the rapid dissolution in a Doppler system. Since SAE signals originate from moving and stationary microbubbles the slow moving microbubbles in the myocardial microcirculation can be detected, which is not possible with conventional Doppler imaging. Because signals from disrupting bubbles are the strongest signals obtained from microbubbles, the sensitivity for detecting microbubbles is much higher using harmonic power Doppler than the harmonic B-scan. Therefore a lower amount of contrast is needed in HPD in comparison to harmonic 2 D echo.

Clinical data is available with several commercially available scanners following intravenous injections of Levovist and Optison. Both agents have been shown to provide a good visualization of myocardial contrast signals in regular patients. Harmonic Power Doppler offers several advantages over harmonic B mode, the most important are the preserved segmentation of myocardial tissue and LV cavity and no need for background subtraction. The excellent delineation of the LV cavity from the myocardium has been used for improved assessment of LV function in patients with suboptimal windows. Algorithms for automatic endocardial border definition are on its way. Myocardial perfusion defects detected by nuclear scans can be displayed by harmonic power Doppler. In acute myocardial infarction infarct size and reperfusion can be assessed. Clinical studies are ongoing to define the role of myocardial contrast echo using harmonic power Doppler in the diagnostics of inducible myocardial ischemia. Doppler power showed a strong positive correlation with the concentration of microbubbles in the blood over a wide range. Using special software off-line analysis of power Doppler recordings easily can be performed.

Wall motion artifacts were the most important limitations in harmonic power Doppler.
They can mimic tissue perfusion signals and have to be avoided by adjustment of the precontrast setting. However, the machine settings, which currently suppress wall motion artifacts, reduce sensitivity for echo contrast as well. Over the last two years there has been a tremendous improvement of signal processing within the echo machine which resulted in a better discrimination of contrast signals from wall motion.

MYOCARDIAL PERFUSION IMAGING - PROBLEMS TO SOLVE AND NEED FOR STANDARDIZATION

Jonny Østensen

Nycomed Amersham Imaging, Oslo, Norway.

Ultrasound contrast agents for myocardial opacification after intravenous injection are now available for research. The main reason for their commercial development is the expected large market if they can demonstrate clinical utility in the diagnosis and evaluation of coronary artery disease.

Myocardial perfusion imaging is a well established technique in nuclear cardiology for noninvasive evaluation of reduced coronary flow reserve during coronary vasodilatation, whereas noncontrast echocardiography use signs of ischemia during inotropic/chronotropic stress to evaluate coronary artery disease.

The new ultrasound contrast agents were received with great enthusiasm since they allowed the cardiologists to "see myocardial perfusion". However, an image that shows that the myocardium is perfused, is not necessarily a myocardial perfusion image. In most patients, we already know that the myocardium is perfused, the question is how well.

One of the problems with ultrasound myocardial perfusion imaging is the lack of a generally accepted definition of the term. Imaging of microbubbles in the myocardium should be called myocardial contrast echo, whereas myocardial perfusion imaging should be reserved to images that are encoded to display at least relative values of regional perfusion or closely related parameters. Obviously, this requires a technique for quantification, and a parameter to quantify. Ten Cate et al. showed that the myocardial contrast disappearance halftime after intracoronary contrast injections was inversely related to coronary flow in dogs [1], and to the coronary artery stenosis luminal area in patients [2]. Rovai et al. demonstrated that colorcoded images of the time to peak intensity correlated well with the regional coronary blood flow [3]. Thus, this technique would deserve to be called myocardial perfusion imaging, although at that time it required intracoronary injections of contrast.

Similar analyses after an intravenous bolus is usually not possible because the bolus is too "slow". This limitation may possibly be circumvented by techniques where microbubbles are destroyed locally by high power ultrasound followed by low power imaging of their reappearance [4].

Another problem with ultrasound contrast myocardial perfusion analyses is the lack of standardization of how quantification should be performed. Videodensitometry is still the most commonly used tool for quantitative analysis of ultrasound images. Unfortunately, a practice of ignoring the logarithmic compression and postprocessing in the imaging systems has become so widely accepted that some journals refuse papers if they do the calculations right (!). Some of the problems ignored by this practice are the following:

- Videointensity is not linearly related to microbubble concentration.
- Quantification at a pixel level is problematic due to motion and speckle variations.
- Regional averaging may produce grossly wrong results; the average of 10 (10dB) and 1000 (30 dB) is 505 (27 dB) and not 100 (20 dB).
- Subtraction of a baseline image does not remove the baseline tissue echo intensity from the difference image, but sometimes removes the contrast intensity (if baseline is high), which is probably not what is intended.

With Sonazoid™, the contrast effect is often more than 10 dB, which means that the baseline signal intensity contributes with less than 10% of the postcontrast signal intensity. Under such conditions, it would be better to ignore the baseline videointensity than to subtract it. This would also remove the problem of alignment of images before subtraction. If images are to be subtracted to evaluate perfusion, a better idea would be to subtract a partial reperfusion image from a complete reperfusion image, since the difference would be inversely related to the rate of microbubble replenishment and perfusion. This and related methods also partially avoid the inherent problems related to differences in attenuation.

Fortunately, the imaging system manufacturers have become aware of the need for and problems related to contrast quantification, and are now providing guidelines and software packages for correct analysis of linearized data. Today these tools are mostly used by interested users for late night data postprocessing. We need an accepted standard protocol for imaging and presentation of parameterized images to develop today's ultrasound machines into ultrasound myocardial perfusion imaging systems.

[1] Ten Cate, F.J. et al. Myocardial Contrast Two-Dimensional Echocardiography: Experimental Examination at Different Coronary Flow Levels. JACC 3(5), 1219-26, 1984.

[2] Ten Cate, F.J. et al. Is the rate of disappearance of echo contrast from the interventricular septum a measure of left anterior descending coronary artery stenosis? Eur Heart J 9, 728-733, 1988.

[3] Rovai, D. et al. Myocardial perfusion by Contrast Echocardiography. From Off-Line Processing to Radio Frequency Analysis. Circulation 83 Suppl III, III-97 - III-103, 1991.

[4] Eriksen, M. et al. Ultrasound Imaging of Tissue Perfusion by Pulse Energy Disruption of Contrast Agent. Patent Application WO 98/47533, 1998.

ASSESSMENT OF NO-REFLOW PHENOMENON AFTER ACUTE MYOCARDIAL INFARCTION USING HARMONIC POWER DOPPLER AND INTRAVENOUS PUMP INFUSION OF LEVOVIST®: COMPARISON WITH INTRACORONARY CONTRAST INJECTION.

L. Agati, S. Funaro, G. Veneroso

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Background: Myocardial contrast echocardiography (MCE) (intracoronary application) has emerged as accurate method to detect "no-reflow phenomenon" after acute myocardial infarction (AMI). In order to investigate the diagnostic value of harmonic power Doppler (HPD) after intravenous infusion of Levovist®, both intracoronary (IC) and intravenous (IV) contrast injections were performed in a group of patients with AMI.

Methods: Seventeen consecutive patients (age 54±7 years) with a first AMI successfully reperfused (Thrombolysis in Myocardial Infarction trial grade 3 flow) within 6 h from symptoms onset by primary PTCA or IV r-TPA were selected for this study. All underwent MCE using HPD (Helwett Packard, Sonos 5500) with Levovist® (400mg/ml, IV pump infusion, trigger intervals 1:4-1:8) and sonicated albumin (0.5-1, ml intracoronary bolus) on day 1 after the achievement of a sustained coronary reflow. Myocardial perfusion was assessed using a 12-segment model (4-2-chambers apical views). A wall motion analysis was performed in the corresponding segments. The endocardial length of the residual contrast defect after reflow was also calculated.

Results: Out of 204 segments, 37 were not analyzed after IVMCE and 44 after IC MCE because of artifacts. ICMCE and ICMCE showed perfusion defect in 31 segments (19%), with a concordance of 89% (kappa coefficient 0.72, CI 0.59 to 0.85). Concordance in anteroseptal , anterolateral and in inferolateral segments was 95% (Kappa 0.92, CI 0.82 to 1), 88% (Kappa 0.66, CI 0.44 to 0.87) and 83% (Kappa 0.57, CI 0.36 to 0.78), respectively. Using ICMCE as reference method, IVMCE had a sensitivity of 74% and a specificity of 93% for diagnosing contrast defects. The extent of no-reflow after IVMCE was 18±19 and after ICMCE was 21±17 (NS).

Conclusion: IVMCE with Levovist® reliably identifies no-reflow phenomenon after successful reperfusion especially in anteroseptal AMI.

THE EFFECT OF BUBBLE DEPLETION ON DESTRUCTION–REPERFUSION FLOW MEASUREMENT WITH CONTRAST

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Dept Medical Biophysics, University of Toronto, Sunnybrook and Womens' College Health Science Centre, Toronto

In a typical destruction-reperfusion measurement of myocardial blood flow using contrast ultrasound, intermittent high MI images are obtained in a sequence of varying intervals. Each image disrupts the bubbles in a region of interest, yielding a signal that reflects the total number of bubbles present. A measurement may involve acquiring five frames separated by a one heartbeat interval, followed by five frames at a two heartbeart interval, and so on up to, say, a sixteen heartbeat interval. The relative signal strength in a region of interest of the myocardium is then measured for each interval and the slope of the resulting function of signal power with time used to estimate the mean velocity of blood flowing into the region of interest. This process forms a simple indicator dilution flow measurement whose indicator is the absence of the bubbles (1-c(t)) where c(t) is the concentration of the bubbles. For the calculation to be valid, the initial value c(0) is assumed to be identical for each pulsing interval. A steady infusion of agent is usually used to provide this.

In order to image the myocardium, the ultrasound beam must pass through the cavities and expose bubbles within them to disruptive ultrasound pressures. The cavity exposure increases as the pulsing interval decreases, so that it is possible that the imaging process depletes the concentration of the bubbles within the circulation by an amount related to the pulsing interval. This would result in a changing intensity of the region of interest due to inadvertant bubble destruction and an incorrect flow estimate.

Method

Using a constant infusion of Definity (DuPont Pharmaceutical Inc), we performed destruction–reperfusion flow measurements of dog myocardium while monitoring bubble concentration in the systemic arterial system. The monitor comprised a femoral artery transducer operating at 5MHz, MI<0.05. Integrated backscatter was calculated using a method that has been calibrated against bubble concentration in vivo and in vitro. In a second series of experiments an attempt was made to adjust the infusion rate so as to achieve an equal baseline enhancement for each pulsing interval. Destruction–reperfusion flow measurements were repeated. Finally, a new contrast imaging method, based on pulse

inversion Doppler (Power Pulse Inversion imaging, ATL Inc) was used to perform the destruction–reperfusion measurements at an MI of 0.1. This avoided the inadvertent depletion artifact.

Results

A 1:1 pulsing interval resulted in a 20 dB systemic enhancement being reduced to 5 dB or less. Even 16:1 pulsing intervals resulted in systemic depletion of bubbles that was detectable. There was a strong correlation between region of interest power and systemic bubble concentration, suggesting that the artifact accounts for a substantial portion of the "reperfusion" curve. In the second series of experiments, it proved impossible to infuse Definity at a sufficient rate and concentration to compensate for the depletion caused at a 1:1 pulsing interval. However, "compensated" destruction–reperfusion measurements gave consistently higher flow values than the uncompensated ones. Power Pulse Inversion imaging caused suffered less from the depletion artifact, so yielded higher flow estimates.

Conclusion

Depletion of the systemic concentration of bubbles by the high MI destruction–reperfusion method may cause a significant error in the resulting flow estimate. This causes the flow estimate to depend on a number of factors related to the measurement protocol, the instrument and the subject, but independent of the flow itself. However, if all of these influences are constant, imaging of areas of relative flow difference (for example ischemic lesions), may still be valid. Online systemic monitoring and compensation of the infusion rate during the measurement may yields more accurate flow values. This is, however, difficult to achieve effectively. A more practical approach to reduction of the systemic depletion artifact may be to use low MI, real time perfusion imaging, such as Power Pulse Inversion imaging.

REAL TIME PERFUSION IMAGING WITH ULTRASOUND CONTRAST AGENTS

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The ultimate purpose of contrast agents is to enhance and aid organ (myocardium, liver, etc.) perfusion studies. Harmonic Doppler and imaging techniques were developed after the introduction of contrast agents to help with the detection of microbubbles in small vessels and capillaries. The harmonic response of bubbles was found to increase with increasing acoustic amplitudes (Mechanical Index, MI), which resulted in rapid bubble destruction. Triggered (intermittent) imaging, insonifying every n cardiac cycles (where n=1,2,3..), was established to minimize destruction and up to now it was the only way to perform a perfusion study. Triggered imaging is cumbersome for the sonographer/clinician and makes replenishment studies a long complicated procedure. In addition, wall motion information is lost. Another drawback of harmonic techniques is the reduced resolution. In order for the harmonic component in the backscattered echoes to be separable from the fundamental, a relatively narrow band signal is transmitted that results in a poorer resolution than fundamental imaging.

Real time perfusion imaging is now possible with a new technique. The technique consists of two components: One is the pulse inversion technique and the other the use of a small amplitude acoustic pressure (MI<0.15). The pulse inversion technique consists of transmitting a series of pulses with every new pulse being the inverse of the previous one and combining the echoes in such a way that the fundamental component is removed before any rf-filtering operation. This method removes the requirement of narrow band transmit for harmonic signal extraction and even in the case of broadband transmit where fundamental and harmonic components overlap the harmonic component is isolated. The small amplitude acoustic pressure serves two purposes: One, is to avoid bubble destruction and to enable real time imaging and two, is to reduce any nonlinear propagation effects in the tissue and generation of a second harmonic component from the tissue which would act as "noise" for the bubble harmonic signals.

The new technique is implemented as both a gray scale mode referred to as Pulse Inversion Harmonic Imaging (PIHI) and a power Doppler mode referred to as Power Pulse Inversion (PPI). In PPI a background tissue image is shown in preferably conventional fundamental mode since at low MI not much tissue harmonic component is present. In the foreground (overlay) of PPI a colorized image of only the harmonic bubble signals is shown. Before contrast injection no color signals are present thus making PPI a real time background subtraction scheme as well.

The amount of fundamental component removal from the echoes with the pulse inversion technique is limited by tissue motion. In PPI a series of pulses (2 or more) are transmitted and then processed in a way to remove tissue motion. The limiting factors in the number of pulses transmitted are the frame rate and bubble destruction. Even at these low MI's some small amount of destruction is present and it increases with repeated insonification. Figure 1 shows bubble echoes and their spectra after processed with the pulse inversion technique. The echoes were calculated with the Gilmore equation for a bubble with 2.5 μm diameter, insonified with a 3 cycle acoustic pulse of 0.02 MPa at 2 MHz, in a medium with speed of sound c=1550 m/s, shear viscosity η=0.003 P, and surface tension σ=0.0725 N/m. In (a) a two-pulse scheme pulse inversion is used where the two echoes are simply added (e_1+e_2) and no motion is present between the pulses. In (b) the spectrum of (a) is shown where the fundamental component at 2 MHz is clearly seen to be eliminated and only the 4 MHz 2nd harmonic is present. In (c) motion equivalent to a time shift of 0.075 of the acoustic wave period is assumed and the two-pulse scheme (e_1+e_2) is used again. In the spectrum (d) there is a strong fundamental component from the motion. In (e) the same motion as in (c) is assumed and a three-pulse scheme is used ($e_1+2e_2+e_3$). With this scheme now the fundamental due to the motion is reduced by about 12 dB as seen in the spectrum (f). This is a simple example to illustrate how applying the pulse inversion technique with more pulses can help in eliminating the tissue motion. More complicated schemes may actually be used in practice.

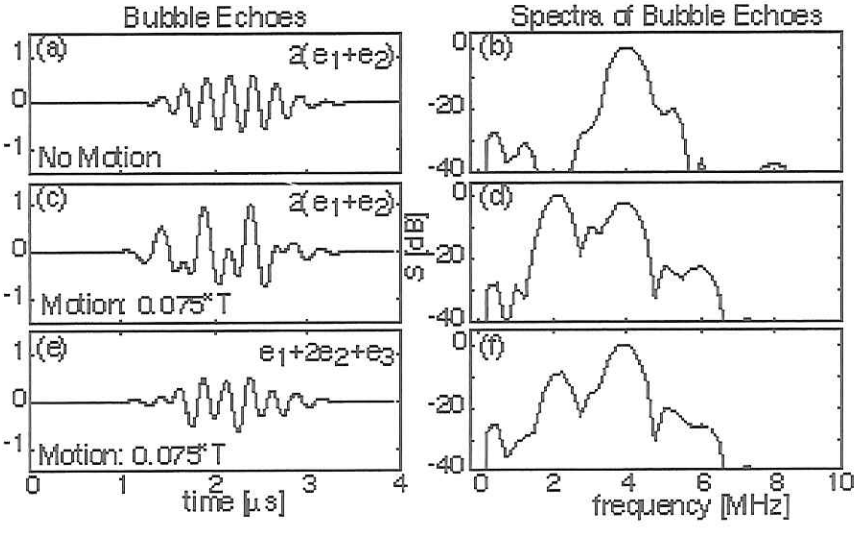

*Figure 1: Bubble echoes and their spectra after pulse inversion processing. (a)-(b) 2-pulse scheme with no motion. (c)-(d) 2-pulse scheme with motion (shift of 0.075*period of acoustic wave). (e)-(f) 3-pulse scheme with motion same as (c).*

In clinical studies with PPI and bolus injections of Optison, good results of myocardial perfusion were observed. At baseline (pre-contrast) there is normally not much signal, with the exception of some residue tissue harmonic depending on the patient. Once the agent enters the left ventricle a strong signal is seen [see Figs. 2(a) and 3(a)] in the cavity but not in the myocardium. Later the deeper regions are shadowed for a few cycles due to high bubble concentrations in the cavity. After a few cardiac cycles the shadowing wears out and the whole myocardium is opacified [see Figs. 2(b) and 3(b)]. In some patients it was observed that the basal septal and lateral wall segments were not as opacified as the apical segments. This is due to the very low amplitudes (MI's) used to achieve real time non-destructing imaging. The basal segments suffer more attenuation due to the presence of both tissue and bubbles above them. However, by adjusting the amplitude to an optimal value good overall opacification may be achieved. In addition from offering real time myocardial perfusion information, PPI also helps in identifying wall motion abnormalities which was not possible before with triggered imaging.

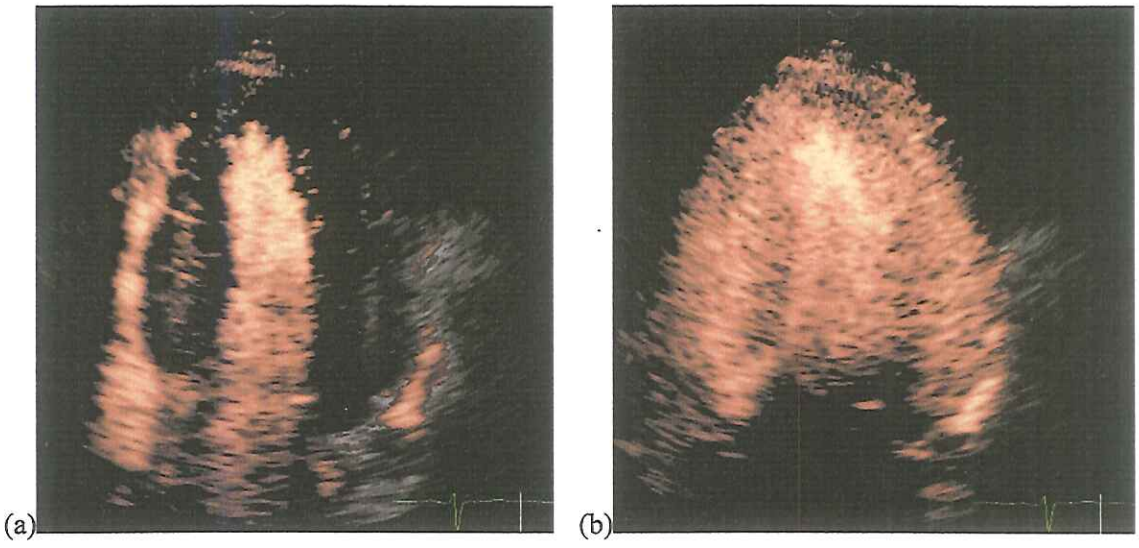

***Figure 2**: Clinical images of myocardial perfusion with PPI. In (a) the contrast just entered the left ventricle and in (b) the myocardium is fully opacified. Both images are at exactly the same part of the cardiac cycle (see white line at ECG traces).*

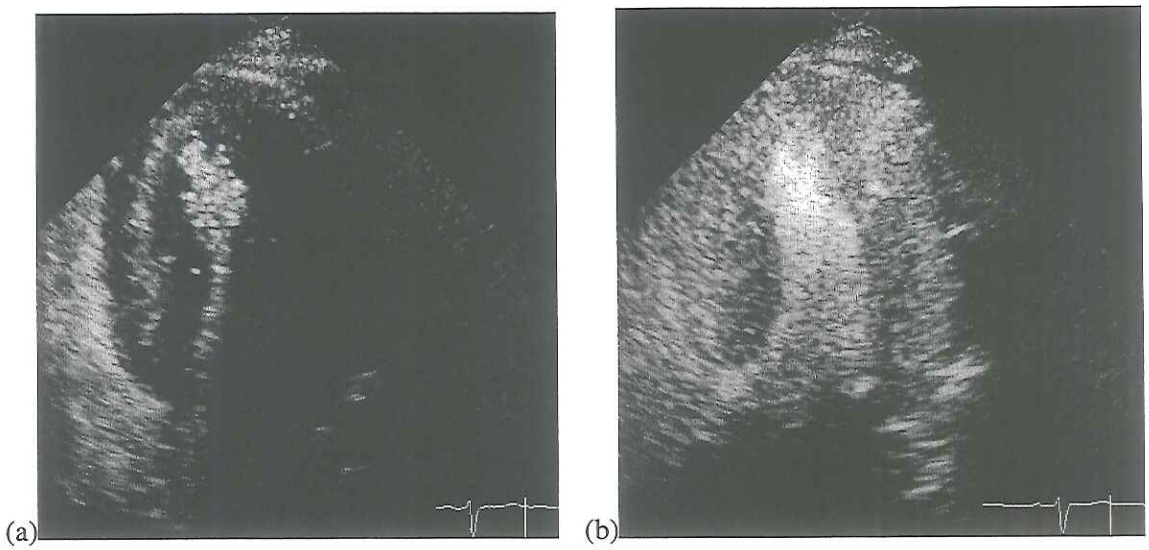

***Figure** 3: Clinical images of myocardial perfusion with PIHI. In (a) the contrast just entered the left ventricle and in (b) the myocardium is fully opacified. . Both images are at exactly the same part of the cardiac cycle (see white line at ECG traces).*

DESIGN OF A PHASED ARRAY TRANSDUCER FOR CONTRAST IMAGING

Nico de Jong[1-2], Ayache Bouakaz[1-2] and Peter Frinking[1]

[1]Department of Cardiology, Erasmus University Rotterdam, The Netherlands and
[2]Interuniversity Cardiology Institute Netherlands, Utrecht, The Netherlands

With the introduction of Ultrasound Contrast Agents (UCA), it was thought that it would be sufficient to detect and image them with conventional imaging methods, currently referred as fundamental imaging. Now it has became clear that new imaging methods, like fundamental imaging, harmonic imaging (grey-scale), harmonic power Doppler imaging, pulse inversion (Doppler) imaging, multi-pulse release imaging, subharmonic imaging etc, are more sensitive to the detect the microbubbles in the presence of tissue.

These newer imaging techniques proved to be more sensitive and are based on specific properties of the UCA. In general, these new characteristics involve non-linear and transient characteristics of contrast agents that appear at the mid and high end of the diagnostic acoustic intensity. All these imaging modalities could be achieved by using the current design of echomachines. E.g. for second and (sub) harmonic imaging the transmission and reception take use of the broad-band capabilities of the transducer. The transient character of the agent is "automatically" detected by Doppler unit. For release-burst imaging a rapid change in the amplitude of the transmitted pule is required, which could be also be realised in current machinery.

Transducer design

Conventional phased array transducer design has been always a trade-off between the number of elements (number of electronic channels) and the quality of the beam-profile. Low number of elements yields an inferior beamprofile with high amplitude of the grating lobe. High number of element results in a low grating lobe level, but much complicated electronic circuitry. Harmonic imaging has shown that beside important elimination of wave aberration, it gives narrower beams and suppressed sidelobes and grating lobes. For harmonic imaging the number of elements, for a given aperture, can be decreased without degrading significantly the image quality. In order to illustrate these features, a numerical algorithm was developed to solve the KZK nonlinear wave propagation equation. The model uses finite differences based on the Alternating Direction Implicit method. The model was validated by experiments carried out with a square single element transducer [1]. Figure 1 shows an example of simulated beam profile generated from an array of five elements operating at 3.8 MHz. Each of the elements is 0.5 mm in width and the pitch is 1.5 mm. The excitation level was 0.4 MPa and the steering angle was set to 0°. The grating lobe level in the fundamental beam (solid line) is

about 12.5 dB below the main lobe level, whereas the grating lobe level in the second harmonic beam (dashed line) is about 23.5 dB below the central lobe.

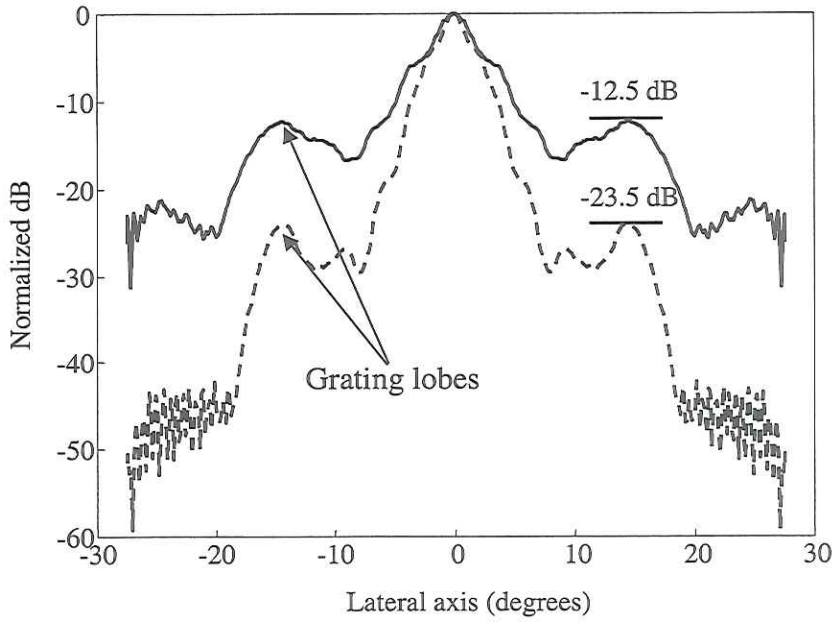

Figure 1: Normalized lateral beam profile for a linear array with five elements, excitation level 400 kPa, z = 48 mm, solid line = fundamental, dashed line = second harmonic.

For contrast imaging, we have developed a special array transducer containing 96 elements. The 48 even elements have a center frequency of 900 kHz and a bandwidth of 45 %, while the 48 odd elements have a center frequency of 3 MHz with a -6 dB bandwidth of 80 %. Both arrays can be controlled independently and can be used in separate transmission and receiving mode. The transducer can be optimized for all the current modalities, e.g. second harmonic by using the low frequency (even elements) for transmission and the high frequency for receiving (odd elements). For simulation purposes, we considered 6 elements from the former array operating at 3 MHz and steered at 20°. The excitation level was 0.21 MPa. Figure 2 shows normalized lateral beam profiles for the fundamental (solid line) and second harmonic frequencies (dashed line) computed at the focus (50 mm). The x-axis is given in degrees. We clearly notice the main fundamental beam located around 20°. However, the grating lobe is located around 40°. In the second harmonic profile, the grating lobe shows much lower energy compared to fundamental grating lobe.

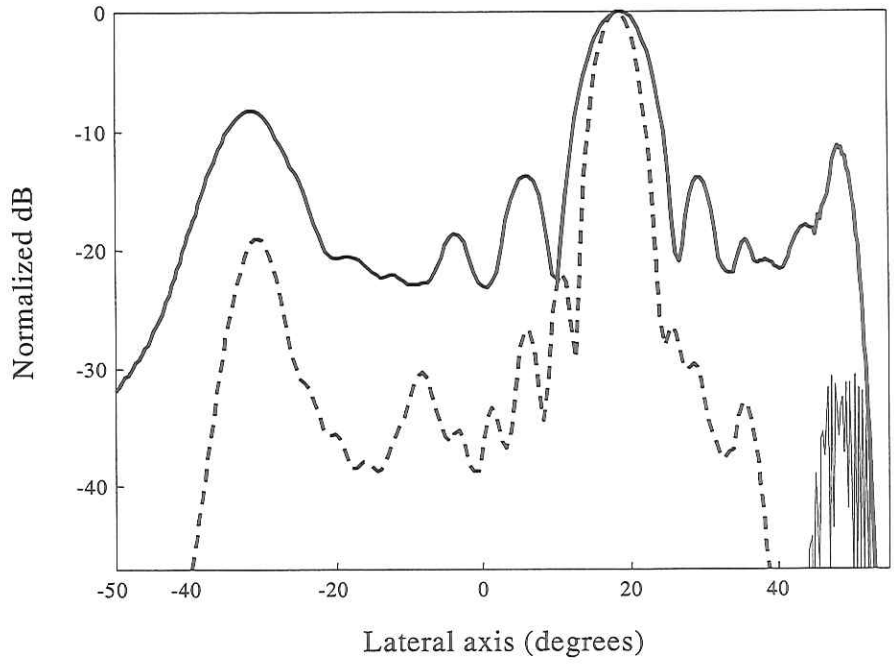

Figure 2: Normalized lateral beam profile for a phased array with six elements, excitation level 200 kPa, steering angle = 20°, z = 50 mm, solid line = fundamental, dashed line = second harmonic.

[1] Bouakaz, A., P. Frinking, et al. (1999). Ultrasound imaging based on nonlinear pressure field properties. 15th Inter Symp Nonlinear Acoustics, Sept 1999, Gottingen, Germany.

OPTICAL VISUALIZATION OF BUBBLES IN AN ULTRASOUND FIELD

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VASCULAR AND PARENCHYMAL ENHANCEMENT OF THE LIVER WITH A NOVEL CONTRAST AGENT

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Both vascular and parenchymal enhancements are important in diagnosing liver diseases, especially liver tumors. Parenchymal enhancement can act as a detection of latent small sized tumors in a high-risk group such as chronic viral hepatitis and cancer bearing patients in other organs. Vascular enhancement can act a role of characterization of the tumors, which were detected with the parenchymal enhancement.

Optimal eradication of microbubbles with sonication promises real time and continuous observation of vascular enhancement. Intermittent flash echo imaging using Optison and delay phase of enhancement using Levovist has brought an instantaneous parenchymal enhancement. How can we obtain a continuous parenchymal enhancement of the liver?

DD-723 (NC100100, Sonazoid), a new ultrasound contrast agent of the third generation is expected to have an ability to indicate not only vascular enhancement in the early phase but also parenchymal enhancement in the delayed phase in the liver.

We have performed a phase 1 clinical trial of DD-723 (Sonazoid) for liver imaging using healthy volunteers and contrast harmonic imaging. The subjects were 20 healthy male volunteers and the age was the twenties including a placebo group of 5 cases. The equipments used were Toshiba Power Vision 8000 and Siemens SONOLINE Elegra. The contrast agent used was DD-723, a stabilized perfluorocarbon microbubble. Three doses were employed with an intravenous injection; the lowest was 0.03 μLMB/kg, the middle was 0.15 μLMB/kg, and the highest was 0.75 μLMB/kg. Vascular imaging of the liver was observed for two minutes after injection and Kupffer imaging was obtained in the delay phase, 5 to 15 minutes after injection from the whole liver.

Results: Arterial enhancement was observed during several seconds and portal enhancement was seen afterward. The parenchymal enhancement of the liver was seen distinctly following vascular imaging especially with the middle dose and more. The staining was seen in the whole liver. The vascular structure was recognized as a defect area of enhancement in the Kupffer imaging because there was almost no contrast agent in the vascular space and microbubbles seemed to be trapped in the liver parenchyma.

DD-723 has a high potentiality for diagnosis of liver diseases. Detection of liver tumor could be performed using the Kupffer imaging in the delay phase and characterization of the tumor is carried out using the vascular imaging in the early phase.

FUNCTIONAL HAEMODYNAMIC STUDIES IN RENAL TRANSPLANTS.

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Two functional microbubble methods were applied to transplant kidneys scheduled for biopsy on clinical grounds, usually because of delayed resumption of function in the post operative period or because of failing renal function in established allografts. The biopsies were performed within 24 hrs of the ultrasound studies and were analysed blind for rejection versus acute tubular necrosis and, in the former category, for the extent of vascular contribution to rejection.

Two microbubble studies were applied. In the first, arterio-venous transit times were assessed by injecting 2.5G, of the 300mg/ml strength Levovist (Schering, Berlin) iv as a bolus followed by a saline flush and examining the spectral Doppler signals from the main transplant artery and vein with a gate placed across both vessels in the renal hilum. The audio outputsof the traces were digitised and fed into a personal computer – the direction separated the arterial from the venous signals. Gamma variate fits were applied to these time-intensity traces and the weighted first moment calculated. The difference between them was taken as the AV transit time. More sophisticated means of measuring `AV transit times are being explored.

In the second component of the study, an infusion of 20mL/hr of Optison (Malinckrodt, St Louis, MO) was set up and, when a steady blood enhancement level was reached (as judged by the signal from a CW transducer placed over a carotid artery), intermittent phase inversion frames were obtained from the parenchyma of the transplant kidney with the probe held still. Intervals of 0.3, 0.5, 2, 3 and 4 sec were chosen based on previous experiments with the same agent in a flowing tank experiment. The B-mode signals were transferred via Ethernet to a PC running HDI Lab (ATL) (Figure) within which the relationship between the signal strength in the renal parenchyma and the triggering interval was analysed to generate interval-intensity curves. The slope of the refill curve was used to assess the refill kinetics.

20 patients were evaluated in the pilot study which indicated that the AV transit was longer in the kidneys undergoing rejection than in ATN (5.5s vs. 4.4s $p < 0.5$ – control values + 3.7s), though there was some overlap. The results of the larger series of 40 patients will be presented.

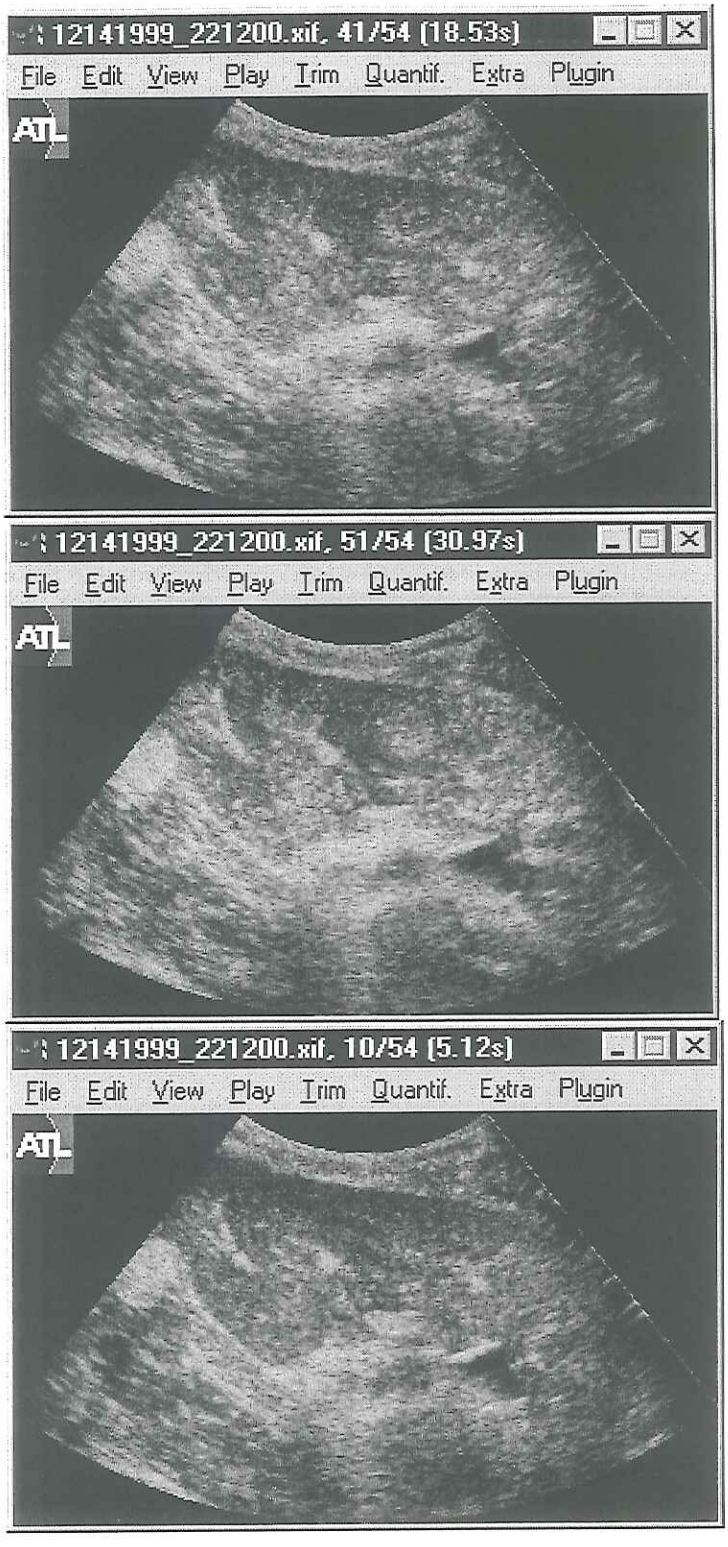

Figure: Frames from one refill kinetics study with triggerred imaging at 0.3 (top), 1 (middle) and 2 (bottom) sec intervals showing the increasing signal from the Optison with longer intervals.

UP-DATE ON LATE PHASE IMAGING IN THE LIVER: PRELIMINARY RESULTS OF A MULTICENTER TRIAL

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Background: The microbubble contrast agent Levovist (Schering AG, Berlin, Germany) has a late liver-specific phase, which can be utilised using non-linear ultrasound methods such as pulse-inversion (PI) ultrasound (US). PI US during the late phase of Levovist shows transient bright B-mode enhancement of normal liver parenchyma. Liver metastases appear as low signal areas within the enhancing liver parenchyma, and preliminary single centre studies have suggested that this is clinically useful in detecting metastatic lesions (1, 2).

We have undertaken an international multicenter study comparing unenhanced B-mode US, Levovist enhanced late phase PI US and dual phase spiral-CT in the detection of liver metastases.

Purpose: We tested the following hypotheses:

1. Levovist enhanced PI US increases the conspicuity of liver metastases in comparison to unenhanced US.
2. Levovist enhanced PI US increases the sensitivity to metastases in comparison to unenhanced US, using dual phase spiral CT as a reference.
3. Levovist enhanced PI US detects smaller metastases than unenhanced US.
4. Levovist enhanced PI US can detect more metastases than spiral CT in selected cases.

Patients and Methods: 146 patients with suspected or known metastases were studied by experienced radiologists using an HDI5000 scanner (ATL Inc, Bothell, WA) and a C5-2 transducer with version 10.1 of the CSI contrast software. The segmental location and size of all visible metastases was charted on baseline imaging (unenhanced fundamental and/or tissue harmonic B-mode). The process was then repeated in PI after a delay of at least 2 minutes from Levovist (400mg/ml) administration, with an ascending dose regime (2.5 followed by 4g if needed). A sweep technique as previously described was used in order to minimise the limiting effects of bubble destruction. The effect on lesion conspicuity of a marker lesion was assessed subjectively by the sonographer as well as quantitatively by a central independent operator using HDI Lab software. The overall number of metastases and the smallest metastasis visible in each patient was recorded on both US modalities at the time of scanning. Comparison was made with helical CT, which was performed in all subjects within 4 weeks of the US using a standardised protocol (150ml contrast material at 300mg/I ml, injection rate: 4ml/s, arterial and portal-venous phase scans, 5mm collimation, 4 mm reconstruction interval). The sonographers were

blinded to the CT findings while the CT readers were blinded to the US findings. In 18 patients additional "platinum standard" imaging (MRI or IOUS) were performed and used to confirm or disprove lesions seen on the other modalities.

Results: The results presented in this abstract are based on a preliminary data analysis and may to a degree differ from the final results that will be presented in the near future.
Lesion conspicuity: The subjective comparison of the conspicuity of the metastases was based on 100 patients. Contrast between normal liver and a marker lesion was improved in 86 patients, unchanged in 8 and decreased in 6. The quantitative analysis was based on the first 47 patients and showed in increase in the difference in echogenicity from 6.8 dB (baseline) to 17.7 dB post contrast.
Sensitivity: Baseline US showed an average of 2.47 overall lesions in keeping with metastases and a mean of 2.22 metastases that were confirmed by CT. Contrast enhanced PI US showed significantly more overall and CT confirmed metastases (mean number 3.87 and 3.34 respectively, $p < 0.01$ for both, (Wilcoxon signed ranks test)). In 54 patients (30%), contrast enhanced PI US showed more metastases than the baseline scan.
Size of detected lesions: In the 54 subjects with new lesions on contrast enhanced US, the smallest lesion size decreased from a mean of 1.49 cm on baseline to 0.75 cm on PI.($p<0.0001$, Wilcoxon SR).
Contrast enhanced US versus spiral CT: In 6/18, at least one extra lesion was seen on contrast enhanced PI that could not be identified on CT, but was confirmed on platinum standard imaging.

Conclusions: PI in the late phase of Levovist increases the conspicuity and the number of metastases visible on US considerably. It substantially decreases the smallest size of lesion that can be detected. It has the potential to reveal lesions that cannot be seen on CT in selected cases. The encouraging results of previous pilot studies were reproducible in a multicenter setting which suggests that the technique can be used in routine clinical practice.

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FUNCTIONAL IMAGING OF RENAL TRANSPLANTS USING CONTRAST-ENHANCED SONOGRAPHY WITH TRIGGERED PULSE INVERSION IMAGING: RESULTS OF A PILOT STUDY

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Ultrasound contrast agent administration improves Doppler signal intensity in the assessment of vascular diseases in renal transplants. However, artifacts can reduce their clinical value. Pulse inversion technique is a new grayscale modality that is expected to improve signal to noise ratio. Qualitative and quantitative comparisons of cortical enhancement using different triggered interval delays (ATL 5000 and HDI Lab software, Bothell, WA) were performed in normal (n=10) and hypoperfused transplants (acute tubular necrosis, acute rejection, infarction) (n=12). Levovist^{R} (Schering, Berlin, Germany) was administrated using continuous infusion at 1ml/mn or bolus technique. Only triggered emission provided significant cortical enhancement with infusion technique, and was considered as optimal at 1 pulse each 4-8 cardiac cycles. Visual evaluation underestimated contrast enhancement, but time intensity curves provided objective information. After bolus injection, peak enhancement was marked, with however some saturation. In pathological cases, contrast-enhanced patterns were correlated with other imaging modalities and pathology.

NEW PERSPECTIVES IN BRAIN PERFUSION IMAGING

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Background and Objectives: Transcranial colour coded sonography (TCCS) is an additional tool in assessing brain tumor morphology and vascularisation. Loss of correlation (LOC) -imaging derived from stimulated acoustic emission (SAE) of ultrasound contrast agents (UCA) and tissue harmonic imaging (THI) are novel perfusion and brain parenchymal imaging methods.
In this pilot-study we tested the efficacy of the albumin based perfluorgas FSO69 in LOC-imaging and compared THI over conventional transcranial sonography (TCS) in tumor imaging.

Methods: Five patients with primary intracerebral tumors were examined before and after bolus-application of FSO69. Perfusion as detected by LOC-imaging technique was correlated to HMPAO-SPECT and diffusion weighted MRI (DWI). In a blinded fashion different examiners compared THI images to conventional TCS images with respect to spatial resolution and tumor texture representation.

Results: Corresponding to MRI morphology hyperperfusion in identified tumor tissue could be visualized with DWI and HMPAO-SPECT. Comparable to these methods time-intensity-curves were demonstrated after echo-enhanced TCCS, positioning the region of interest (ROI) in the suspected tumor area.

Conclusions: Using THI and LOC we are able to demonstrate that tumor morphology (size) and perfusion may be sufficiently assessed. The sensitivity of sonographic diagnosis of intracerebral neoplasms as well as the quantification of its perfusion may be improved by the use of an albumin based perfluorgas UCA.
In summary, the i.v.-administration of UCAs allows the measurement of perfusion abnormalities of normal brain parenchyma and tumor tissue, suggesting it to be comparable to SPECT and diffusion weighted MRI.

THE MECHANISM OF PARENCHYMAL ENHANCEMENT OF THE LIVER BY MICROBUBBLE-BASED ULTRASOUND CONTRAST AGENT: AN INTRAVITAL MICROSCOPY STUDY

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Background: Although some agents are known to be phagocytosed by the Kupffer cells on delayed phase imaging (>5min), most agents have a parenchymal enhancement phase after the agent has cleared the blood pool for as yet unknown reason.

Purpose: To clarify the mechanism of entrapment of AF0150 within the liver using intravital microscopy.

Materials and Methods: Eight Sprague-Dawley rats were used for this study. Six of the 8 rats, received 0.05 ml of Fluoresbrite™ plain YG microspheres (0.9410 μm ± 0.0140 μm) (Polysciences, Inc., Warrington, PA) through the tail vein in order to label Kupffer cells. 24-hours later, rats were anesthetized with ketamine and acepromazine cocktail (5:1 ratio). After a midline abdominal incision, the left lobe of the liver was exteriorized onto a microscopy stage. Krebs-Henseleit Solution at 37 °C was dripped to provide the fluid necessary for the water objectives. Fluoresbrite microspheres were observed under fluorescence (Excitation Wavelength 450 to 490 nm / Emission Wavelength >520nm). The liver was transilluminated with a 50-watt monochromatic halogen bulb with heat filters using 25x and 60x water immersion objectives. 2 to 3 ml of AF0150 (Alliance Pharmaceutical, La Jolla, CA) was injected through the tail vein. All images were recorded to S-VHS videotapes. Data analysis and measurements were performed off-line. The distribution and number of Kupffer cells labeled with microspheres was determined. The distribution and number of stationary microbubbles in the sinusoidal lumen was defined. The number of microbubbles, which seem to attach to Kupffer cells, was determined.

Results: The microbubbles were clearly seen under white light transillumination. Some microbubbles became stationary in the sinusoids and were either dislodged a little later or shrunk and disappeared in several minutes. The distribution of the microbubbles was fairly homogeneous in comparison to the fluorescent labeled-microspheres, which appeared to be heterogeneously distributed and most were observed to be located at the periportal area (zone1). Few bubbles became stationary just beside the fluorescent labeled cells.

Conclusions: We directly observed the microbubbles with intravital microscopy. The microbubbles became temporarily stationary in the sinusoids and were fairly homogeneously distributed in contrast to distribution of the fluorescent-labeled phagocytes. We conclude that the majority of AF0150 microbubbles are trapped in the sinusoidal lumen rather than phagocytosed by the Kupffer cells.

LOW CONTRAST DOSE REFLUX - SONOGRAPHY IN CHILDREN WITH PHASE INVERSION IMAGING

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Background : Darge[1] has recently introduced Reflux- Sonography as a suitable alternative to Micturating Cystography (MCU) in the detection or exclusion of vesico-ureteral- reflux (VUR). He suggested a contrast agent (Levovist) dose of 10 % of the bladder volume. That means a contrast dose of approximately 10 to 30 ml would be required in most children. At this dose the cost for ultrasound contrast agent is higher than that for iodinated contrast agents used for MCU.
This study was undertaken to assess if the use of phase inversion ultrasound (PI US) has advantages over fundamental ultrasound and if PI US allows a reduction of contrast agent dose and improves cost-effectiveness in this application.

Materials and Methhods : 31 children with 64 kidney - urteter - units (KUU) for investigation of VUR underwent Reflux-Sonography which was followed by MCU. After scanning the urinary tract the bladder was filled with normal saline. Then Levovist was added in 2 ml portions until an optimal image quality was obtained. The kidneys and distal ureters were examined before, during and after micturation in fundamental US and PI US for reflux. Reflux was diagnosed when microbubbles appeared in the ureter or kidneys. The results of Reflux Sonography in fundamental US, PI US and of MCU were compared.

Results : In 1 case we administered 3 ml of Levovist, in 6 children 4 ml was used, in 2 cases 5 ml , in 6 patientes 6 ml, in 14 children 8 ml and in 2 cases 16 ml contrast agent was added into the bladder. The average Levovist dose per patient was 7 ml. Reflux was seen on at least one of the three modalities in 12 KUU. Fundamental US showed reflux in 8, PI US in 10 and MCU in 8. In 6 KUU reflux was concordantly observed in all three modalities. VUR was shown by US only in 4 KUU, in 2 of these it was only demonstrated on PI but not on fundamental. In two cases reflux was shown on MCU only. In 8 KUU reflux was observed on at least 2 modalities, in 7 of these there was agreement in regard to the grading of the severety of reflux. In one case PI US revealed a grade IV reflux whereas fundamental US underestimated this as a grade I.

[1] K.Darge et al., Radiology 1999; 210: 201 - 7

Conclusions : PI US provided considerably stronger enhancement than fundamental US and achieved excellent image quality even at low contrast dose.

In our preliminary series PI US was more sensitive in detection of vesico-ureteral reflux than fundamental US and MCU. Reflux-Sonography with PI can be performed at low contrast dose and thus at lower cost.

OBSERVATION OF THE BEHAVIOR OF MICROBUBBLES EXPOSED TO ULTRASOUND USING A HIGH-SPEED CAMERA

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Introduction Ultrasound contrast agents (UCAs) greatly improve the image quality of diagnostic ultrasound equipment, and clinical applications have been widely studied in recent years. Miller et al. reported enhancement of cavitational bioeffects due to UCAs [1], but its mechanisms are still unclear. The dynamics of microbubbles are still not well understood, because it is difficult to observe microbubbles with diameters of only a few microns that oscillate at the frequency of ultrasound. Dayton et al. used a high-speed camera to observe the behavior of microbubbles [2], but the frame rate of the observation was limited to less than 1,000 frames/s. In this study, we developed a new high-speed observation system [3] with a maximum magnification of x 100 and maximum imaging rate of 2 x 10^7 frames per second, and we observed the dynamic behavior of cavitation bubbles produced by ultrasound and the behavior of gas-containing microbubbles and UCA (NC100100) bubbles exposed to ultrasound.

Method

System for observation of cavitation bubbles A new system was developed for observing cavitation bubble produced by exposure to focused CW ultrasound in water. The maximum imaging rate of the high-speed camera (Nac: ULTRANAC) was 2 x 10^7 frames/s, and the maximum optical magnification was x 100. A xenon flash lamp with a simple focusing lens was used as the high-intensity light source. A focused PZT transducer of 250 kHz in center frequency was used as the ultrasound source. The dimensions of the transducer were 110 mmin aperture and 150 mm in focal length, and the acoustic pressure was 0.3 MPa. The optical focuses of a microscope object lens and an illuminating flashlight condenser lens were both set at the spot where cavitation bubbles were generated.

System for observation of gas-containing microbubbles and UCA bubbles We also developed a system for observing gas-containing microbubbles and UCA bubbles. This system is basically the same as that for observation of cavitation bubbles except for the following points. A different high-speed camera (IMACON790, Hadland Photnics), the maximum imaging rate of which was 2 x 10^7 frames/s, was used. A focused transducer of 1 MHz was also employed. The dimensions of the transducer were 50 mm in aperture and 70 mm in focal length, and the acoustic pressure was approximately 0.5 MPa. In this system, we used pulsed ultrasound and synchronized ultrasound

exposure and shutter triggering of the high-speed camera. We also used a new optical system for the illuminating light source to achieve maximum magnification of x 100 at a higher imaging rate.

We used two types of gas-containing microbubbles, PVC (polyvinyliden chlonde acrnitorile)-shelled microbubbles (Matsumoto, F-30E) and albumin-shelled microbubbles, and UCA (Nycomed, NC100100). The diameters of the PVC-shelled microbubbles and the albumin-shelled microbubbles were about 20 mm and 20–100 mm, respectively. NC100100 is an agent of PFC (perfluorocarbon)-filled microbubbles stabilized with surfactant, and its diameter is 3–5 mm.

Results

Behavior of cavitation bubbles Figure 1 shows high-speed photographs of cavitation bubbles generated by the negative pressure of ultrasound. The actual imaging rate was 2 x 10^6 frames/s (0.5 ms/frame, 8 frames/cycle) with optical magnification of x 15. Periodic expansion and shrinkage of cavitation bubbles were observed in every 8 frames, and this time interval corresponded to the ultrasound frequency (250 kHz). The maximum diameter of a cavitation bubble in the expansion phase was about 10 mm, but the bubbles were too small to observe in the compression phase.

Behavior of gas-containing microbubbles and UCA Figure 2 shows the behavior of PVC-shelled microbubbles exposed to ultrasound of 250 kHz. The imaging rate was 2 x 10^6 frames/s (0.5 ms/frame, 8 frames/cycle) with magnification of x 66. Changes were observed in the diameter of the bubble in the lower right corner of each photograph. It is also observed that a portion of the bubble irregularly deformed in the compression phase (Fig. 2-d, e), and rupture of the bubble shell was captured. The diameter of the bubble in the expansion phase was about three-times larger than that in the compression phase, and the moving speed of the air-water boundary of the bubble was several tens of meters per second.

Figure 3 shows the behaviors of the albumin-shelled microbubbles exposed to ultrasound of 250 kHz. The imaging rate is 2 x 10^5 frames/s (5 ms/frame, 4 frames/5 cycles) with magnification of x 25. In these photographs, the microbubble indicated by an arrow grows gradually (Fig. 3-a, b), reaches a critical size (Fig. 3-c), and then collapses (Fig. 3-d). Other bubbles showed the same behavior, but the phases of expansion and collapse were different. This behavior was periodically repeated.

Figure 4 shows the fragmentation of microbubbles exposed to ultrasound of 250 kHz. The imaging rate was 2 x 10^5 frames/s (5 ms/frame, 4 frames/5 cycles) with magnification of x 33. In this series of photographs, bubbles are fragmented into small bubbles in the compression phase and absorbed into a one large bubble in the following expansion phase.

The behavior of UCA bubbles exposed to 1-MHz ultrasound is shown in Fig. 5. The imaging rate was 1 x 10^7 frames/s (0.1 ms/frame, 2 frames/cycle) with magnification of x 50. Cyclic expansion and shrinkage of several UCA bubbles (one bubble is indicated by an arrow) was observed, but it was difficult to observe detailed behavior because the optical magnification was not sufficient.

Discussion Generally, microbubbles exposed to ultrasound repeatedly expand and shrink, and they grow gradually. After several expansion-shrinkage cycles, the diameter of a bubble reaches a critical size, and then the bubble collapses. In the case of albumin-shelled microbubbles of about 50 mm in diameter, the time period of growth and collapse was 4 cycles and the critical diameter was approximately two to three times larger than the initial diameter of the microbubble. In our experiment, the cavitation bubbles shrank to an invisible size in the compression phase, whereas the gas-containing microbubbles maintained a visible size. The difference between the cavitation and gas-containing microbubbles is that the former contain water vapor and the latter contain almost insoluble gas. In the case of cavitation, water vapor in the bubble is easily condensed back to water in the compression phase, and therefore the diameter of the bubble decreases. The decrease in bubble diameter causes an increase in shrinking force due to surface tension. Hence, the bubble shrinks drastically, and a very high temperature and pressure are produced at the center of the bubble.
In the case of gas-containing bubbles, compressed gas produces a rise in pressure and the bubble diameter reaches a new equilibrium state at a smaller diameter. However, anisotropic contraction and fragmentation of gas-containing bubbles was observed, as shown in Figs. 2 and 4, and further study is needed to understand bubble collapse of UCA.

Conclusions We developed a new observation system using a high-speed camera and a microscope for observation of the behaviors of cavitation bubbles, gas-containing bubbles and ultrasound contrast agent bubbles. Under practical measurement conditions, the maximum imaging rate was 1×10^7 frames/s with optical magnification of x 50 and 2×10^6 frames/s with optical magnification of x 100.

Acknowledgements The authors thank Prof. Nakao of Muroran Institute of Technology for his help in the use of the high-speed camera. This research was partially supported by a grant-in-aid for scientific research from the Ministry of Education, Science, Sports and Culture, Japan and was carried out as a part of the activities of the Working Group, Safety Committee, the Japan Society of Ultrasonics in Medicine.

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[3] K. Kuribayashi et al., "A high-magnification and high-speed system for the observation of microbubbles under ultrasound exposure,"1999 IEEE Ultrasonics Symposium Proceedings, in print, 1999.

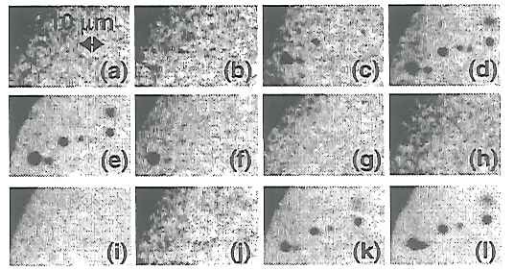

Fig. 1. High-speed photographs (8 frames/cycle) of cavitation bubbles produced by 250-kHz ultrasound.

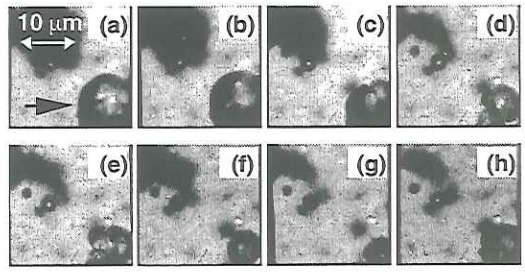

Fig. 2 . High-speed photographs (8 frames/cycle) of PVC-shelled microbubbles.

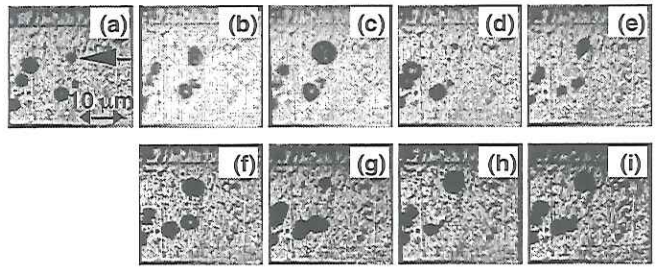

Fig. 3. High-speed photographs (4 frames/5 cycles) of albumin-shelled microbubbles.

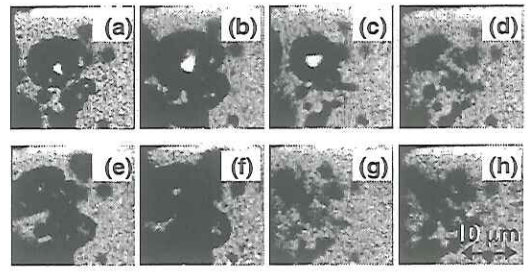

Fig. 4. High-speed photographs (4 frames/5 cycles) of PVC-shelled microbubbles.

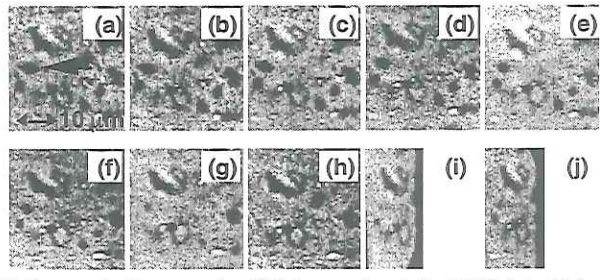

Fig. 5. High-speed photographs (10 frames/cycle) of UCA bubbles.

IMPROVED SONOGRAPHIC DETECTION OF LIVER METASTASES WITH CONTRAST ENHANCED WIDEBAND HARMONIC IMAGING

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Purpose: We want to assess whether the contrast enhanced wideband harmonic imaging ultrasound during the late liver specific phase with Levovist can improve the detection of liver metastases compared to the nativ ultrasound.

Methods: The liver of 86 patients with a malignant disease(21 colon carcinoma, 15 breast carcinoma, 8 bronchial carcinoma, 6 pancreas carcinoma, 5 malignant malignoma and 31 other malignant diseases) where scanned with a Sonoline Elegra (Siemens, Issaquah, WA) with a 3,5 MHz transducer. All patients where first scanned with a normal ultrasound in fundamental B- mode. After this Levovist(Schering AG, Berlin) was injected and a second scan in wideband harmonic imaging was performed after a period of 2,5 minutes. In 71 patients one injection was sufficient, in 15 patients a second injection was needed. Per injection 2,5 g Levovist(n= 82) or 4 g(n= 19) Levovist was given. All patients had a goldstandard examination. This was in 35 cases Spiral CT, 16 dynamic CT, 14 MR, 14 Intraoperative Ultrasound and 7 Endorem MR. The goldstandard was controlled by a blinded reader. If there was a difference to our assessment other modalities like follow up examinations or histology results were consulted and a consensus reading was done.

Results: From our 86 patients, 52 patients had liver metastases on the goldstandard examination. The fundamental ultrasound showed 48 patients with liver metastases and the contrast enhanced ultrasound showed 51 patients with liver metastases.
In 34 patients(47%) the contrast enhanced ultrasound showed more lesions then the native ultrasound. These new detected metastases were often very small. There were two false positive lesions on the fundamental ultrasound and we had 7 patients where we saw false positive lesions on the contrast enhanced ultrasound compared to the reference examination. Nearly on every patient we got the impression that it is more easy to see metastases on contrast enhanced wideband harmonic imaging although we could not identify new ones in every case.

Conclusion: The contrast enhanced liver sonography dramatically improves the detection of liver metastases. Specially small lesions can be visualized with this method.

BRAIN PERFUSION IMAGING USING CONTRAST AGENT SPECIFIC IMAGING MODES

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Introduction

Although contrast agents enable the visualization of vascular blood flow in color or power mode even under unfavorable imaging conditions, many issues related to ultrasound-based perfusion imaging are still not solved. The clinical value of ultrasound perfusion imaging, however, would be considerably high, since many diseases, like infarctions and tumors, are linked to perfusion abnormalities. Cardiac infarctions and strokes, which are infarctions in the brain, are among the leading causes of death in industrialized countries. Validated proportional indicators of cerebral blood flow and potential diagnostic tools are Tc-HMPAO-SPECT, PET and diffusion weighted MRI [1]. Compared to ultrasound [2], these methods are time consuming, require radioactive tracers, or are intolerable for critically ill or restless patients.

The flow velocities associated with perfusion are too low to be measured *in vivo* with Doppler-based ultrasound techniques. A different approach is to evaluate time-intensity-curves (TICs) acquired after a bolus injection of contrast agent. A TIC reflects, how the mean intensity (brightness) of a region of interest (ROI) changes over time. The time span of typically 1-5 minutes covers the wash-in and the washout of the contrast agent. To achieve a sufficient sensitivity, contrast agent specific imaging modes are necessary. It is evident that TICs inherit all sources of artifacts from the imaging techniques they are based on. Moreover, the quality of TICs generally suffers from artifacts that are due to motion and to the heart cycle, especially if ECG-triggering is not available. A very robust algorithm is needed to automatically extract parameters, e. g. the peak intensity over baseline, the contrast arrival time and the duration of enhancement.

In this presentation, we will show preliminary *in vivo* results of brain perfusion imaging studies. Three different imaging modes, (1) contrast harmonic imaging (CHI), (2) contrast burst imaging (CBI), and (3) time-variance imaging (TVI) were investigated. TICs for ROIs corresponding to the thalamus, the lentiform nucleus, and the white matter could be determined reliably. Furthermore, the complete imaging plane was divided into resolution cells of 1 mm by 1 mm. The evaluation of the TICs corresponding to these resolution cells leads to the formation of parameter images visualizing e. g. the peak intensity.

Contrast Harmonic Imaging

Contrast harmonic imaging transmits a pair of pulses per beam line, where the two transmit pulses are 180 degrees out of phase. The sum of the resulting echoes consequently equals zero, if the observed scatterers are linear, stationary and time-invariant. Signal components resulting from even-order non-linearity will be detected without a loss in bandwidth, since no filtering is necessary [3]. This technique is also sensitive to changes in the acoustic properties of the insonified microbubbles ("bubble destruction"). CHI images also show the effects of nonlinear sound propagation in tissue resulting in a tissue harmonic image. This background image facilitates the orientation, but makes it more difficult to visually detect changes in the image brightness that are due to the wash-in and washout of the contrast agent.

Contrast Burst Imaging (CBI), Time-Variance Imaging (TVI)

Contrast burst imaging and time-variance imaging are designed to sensitively detect the changes in the acoustic properties of insonified microbubbles. Both techniques use sequences of broadband high energy pulses. A high pulse repetition frequency of more than 5 kHz is chosen in order to minimize motion artifacts. The CBI and TVI sequences typically consist of 6 pulses and 10 pulses, respectively.

Contrast Burst Imaging

CBI is derived from power mode. The high pulse repetition frequency in combination with a wall filter suppresses the tissue signal and also most flow signals. Processes that are associated with the destruction of microbubbles produce broadband noise in the Doppler spectrum. Consequently, a part of this noise signal will fall into the pass band of the wall filter and will be displayed.

Time-Variance Imaging

Time-Variance imaging extracts the amplitude and the "spectral slope" from the N echoes acquired per beam line [4]. The spectral slope is a parameter that describes the asymmetry of the RF spectrum with respect to the center frequency. At a given position, N measurements for each of the two parameters describe the changes in the acoustic properties of the observed scatterers. Since destructive processes are manifold, there are no easy rules predicting whether e. g. the amplitude of the backscattered signal should increase or decrease. Therefore, a stochastic evaluation was implemented to process the measured data in order to form an image that indicates the presence of contrast agent.

Extraction and Evaluation of Time-Intensity Curves (TICs)

To characterize perfusion conditions based on the analysis of TICs, a model function is fit to the measured curve in a least mean square-sense as shown in Fig. 1. From this model function, characteristic values, like the peak intensity and the peak time (contrast arrival time), are calculated. The curve fitting greatly improves the robustness of the analysis, even though the optimization of 5 parameters is a complex task. The parameters are determined iteratively. Initial values are calculated based on general assumptions and on a coarse analysis of the measured data. In experiments, the proposed curve fitting outperformed various types of filtering methods we investigated.

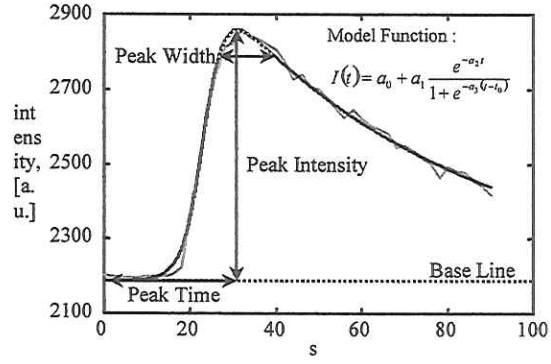

Fig. 1: Model function $I(t)$ fitted to measured time-intensity curve.

Formation of Parameter Images

The sensitive detection of contrast agent using CBI or TVI and the parameter extraction technique described above made it possible to reduce the ROI size to 1 mm by 1 mm. Taking into account that transcranial imaging is performed with transducers in the 2-3 MHz range and that motion artifacts can hardly be avoided when imaging manually over several minutes, this ROI size can be considered minimal. A parameter image, where the color of the ROIs codes the value of a selected parameter, facilitates the interpretation of the information extracted from the TICs.

Experimental results

Experiments were conducted on healthy volunteers. After an injection of Levovist®, sequences of 45-70 images were acquired at a frame rate of 0.5 Hz. Scanning was performed with a 2.5 MHz phased array through the transtemporal bone window at an angle of 10 degrees so that the thalamus is in the imaging plane. The field of view was set to a 90 degrees sector with a depth of 10 cm. CHI images were acquired in parallel with CBI or TVI images. The CHI images help the examiner to keep the imaging plane. However, the quality of

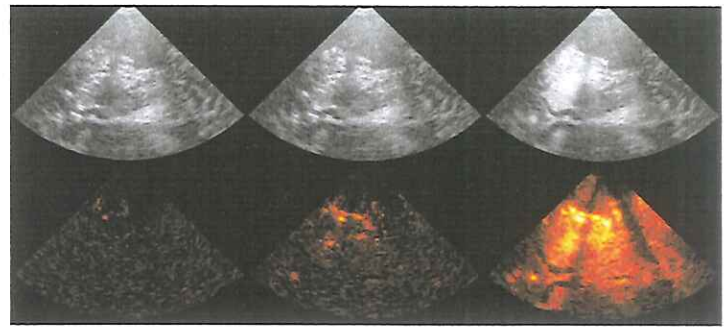

Fig. 2: CHI images (top row) and TVI images (bottm row), 0 s, 10 s, and 16 s after injection of Levovist®.

the CHI images is degraded by the parallel acquisition of the CBI or TVI images. Moreover, the power for the CHI mode was reduced with respect to the default value to have optimal conditions for CBI and TVI. While CHI and CBI are available on the system in real time, the TVI images had to be processed offline from digitally recorded base band data.

All experiments yielded TICs similar to the one shown in Fig. 1. CBI and TVI performed better than CHI making possible the formation of parameter images. A peak intensity-image calculated from a TVI sequence is shown in Fig. 3. Fig. 2 and Fig. 3 represent the same experiment in order to allow a direct comparison. The peak intensity image clearly reflects anatomic structures based on the perfusion conditions. The two dark sectors, which affect the CHI and the TVI images, probably have anatomic reasons.

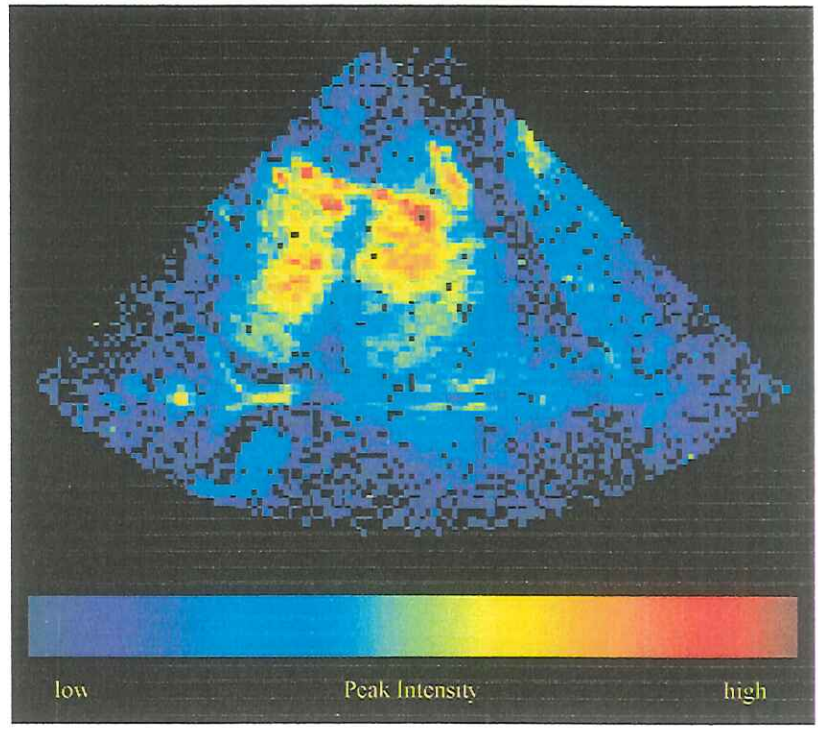

Fig. 3: Parameter image. Peak intensity. Calculated from a series of TVI images.

Discussion

All investigated imaging modes showed a high sensitivity for the detection of contrast agent. While CHI clearly shows anatomic structures, which have far less contrast in B-mode, the assessment of perfusion conditions based on the visual impression is difficult. CBI and TVI display the information in an easy-to-interpret way. In order to decide which imaging mode provides the highest sensitivity or the best SNR, further investigations will be necessary. In our experiments, differences between CBI and TVI turned out to be marginal. A reason for this similarity might be the fact that motion artifacts during the acquisition of a single beam line and shadowing caused by the contrast agent were not an issue for this application.

The proposed algorithms for the evaluation of time-intensity curves enabled the formation of parameter images. Clinical studies have to be conducted to explore the value of different parameters. In combination with CHI images, which are at the same time tissue harmonic images, parameter images have the potential to greatly facilitate the diagnosis of perfusion abnormalities in the brain.

[1] G. Rordorf, W. J. Koroshetz, W. A. Copen, S. C. Cramer, R. F. Budzik, L. H. Schwamm, F. Buonanno, A. G. Sorensen, G. Gonzalez, "Regional ischemia and ischemic injury in patients with acute middle cerebral artery stroke as defined by early diffusion-weighted and perfusion-weighted MRI," Stroke; vol. 29, 1998, pp. 939-943.

[2] Th. Postert, A. Muhs, S. Meves, J. Federlein, H. Przuntek, Th. Büttner, "Transient response harmonic imaging: an ultrasound technique related to brain perfusion," Stroke, vol. 29, 1998, pp. 1901-1907.

[3] P. Jiang, Z. Mao, J. C. Lazenby, "A new tissue harmonic imaging scheme with better fundamental frequency cancellation and higher signal-to-noise ratio," in Proceedings of the IEEE Ultrasonics Symposium, 1998, pp. 1589-1594.

[4] W. G. Wilkening, J. C. Lazenby, H. Ermert, "A new method for detecting echoes from micro-bubble contrast agents based on time-variance," in Proceedings of the IEEE Ultrasonics Symposium, 1998, pp. 1823-1826.

OPTIMIZATION OF AN ULTRASOUND CONTRAST AGENT : AN *IN VITRO* STUDY OF ITS STABILITY AS A FUNCTION OF CONCENTRATION, TIME SINCE RECONSTITUTION AND OUTPUT POWER

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Stable, optimized and reproducible agent activation is of primary importance for reliable visual image enhancement and the development of quantitative techniques using ultrasound contrast agents (USCA). This study used measurements of the attenuation of contrast solutions (a parameter inherently linked to the size, number density and acoustic response of microbubbles) to characterize microbubble stability and to relate the level of stability to the concentration of the original solution, the time since reconstitution and the insonification power.

Levovist® (Schering AG, Berlin, 2.5 g vials) was reconstituted at concentrations of 200 mg/ml, 300 mg/ml and 400mg/ml with sterilized water following the recommended protocol. Doses (0.1 ml, 0.5 ml and 1 ml) of each of these solutions were injected into a cylindrical measurement cell filled with 0.9 % room-temperature saline solution and agitated with a magnetic stirrer. For each dose and solution concentration, independent injections were made at 2, 12, 22 and 32 minutes following reconstitution. The signal loss across the cell was measured in the range of 2 to 5 MHz using a broadband through-transmission technique (5 MHz center-frequency Panametrics transducers, insonification rate of 1.6 pulses per second). The effect of two different ultrasound powers on the microbubbles was investigated by changing the damping on the pulser-receiver such that at one damping the pulse had a maximum power 6 dB higher than for the other damping.

For each solution concentration and dose, the attenuation measured immediately following injection at 2, 12, 22 and 32 minutes following reconstitution was fit to a decaying exponential ($f(x) = f(0) \cdot e^{-nx}$). The exponential decay rate was 3.3 ± 0.7 times higher for the doses extracted from the 200 mg/ml solution than from the 400 mg/ml solution and 1.8 ± 0.4 times higher for the doses extracted from the 300 mg/ml solution than from the 400 mg/ml solution. The attenuation as a function of insonification time was fit to a negative power law ($f(x) = a \cdot x^{-n}$). The rate of decay was consistently faster when the solution in the measurement cell was exposed to the higher power pulse than for lower power insonification. For injections of the 300 mg/ml solution the rate of decay was 4.4 ± 0.7 times higher for the higher power insonification.

The average attenuation (2 to 5 MHz) across the cell immediately following injections of 0.5 ml of 400 mg/ml was 2.4 ± 0.4 dB/cm higher than following injections of 1 ml of 200mg/ml. This difference may be attributed to different rates of microbubble decay within the vial following reconstitution. The 400 mg/ml concentration provides the strongest initial acoustic response, and the microbubbles decay less rapidly in the vial. At the beginning of the attenuation decay curves the maximum attenuation is obtained with the high power pulse, but at later time the residual attenuation is higher for the solution insonified at lower power. This suggests that a higher power impulsion should be used to obtain a strong acoustic response for a single pulse or if the contrast product in the imaged region is renewed by perfusion between pulses. An initially weaker but more sustained response may be obtained with a lower insonification power.

CAUSALITY AND BOUNDED PULSE PROPAGATION IN BUBBLY LIQUIDS

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This paper reviews the constraints imposed by the law of causality (which is, of course, obeyed by any real physical system) on bounded pulse propagation in bubbly fluids and considers the implications for medical ultrasound imaging systems, with emphasis on potential image artefacts. The problem is important because of the great interest in contrast agents: the linear propagation of ultrasonic waves in a liquid containing micro bubble contrast agent can exhibit marked velocity dispersion depending on the volume of the mixture occupied by bubbles, and the size distribution of the bubble population. Medical ultrasound imaging systems typically employ the use of broadband imaging pulses. Most conventional contrast agents exhibit resonance behaviour within the frequency range of these imaging systems. It is shown that causality has some unexpected consequences for propagation in this type of medium. Unlike most other physical laws, causality does not possess a universal exact mathematical prescription, and is often just stated as "the effect can not precede the cause". Some simple models are briefly considered in order to define its influence on medical ultrasound pulses in a mathematically pragmatic way. Illustrative examples are presented from both in vitro water bath experiments and the results of numerical simulation. The full three spatial dimensional nature of the propagating pulse is considered and it is shown that for typical fields employed in imaging diffraction, effects can lead to an apparent 'super-luminal' behaviour of the propagating pulse, i.e. certain signal components may appear to have a velocity greater than the sound speed. An effective method to calculate phase velocity from transmission measurements, which can overcome the phase unwrapping ambiguity, is also given.

IMPROVING TRANSMIT POWER UNIFORMITY

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It has been previously demonstrated in animal studies with ultrasound contrast agents, that measurement of myocardial blood flow is possible by altering the ultrasound pulsing interval using high-MI triggered imaging[1]. These studies have been performed using open-chest dog models and with a short-axis imaging plane. In humans, the results of this technique, although promising, have not been quite as good. In order for this quantification technique to be accurate, microbubbles must be destroyed uniformly throughout the area of interest. Humans have far greater attenuation of ultrasound energy than open-chest dogs. Additionally, the larger heart size and the use of the apical-four chamber view make the region over which the power should be constant much larger on humans. The combination of these factors make flow quantification difficult in practice. Although a purely uniform power field is clearly an unattainable goal, there is much potential to improve the current situation. Transducers and systems were not previously designed with transmit uniformity as a goal. For quantification of perfusion to become more robust, equipment manufacturers will need to develop products with transmit uniformity in mind.

There are several areas that can be looked at to improve the situation, including new transducers, system changes, more sensitive detection techniques and improved contrast agents. New transducers can be designed having apertures and elevation foci consistent with a uniform power field (i.e., deeper focuses). Additionally, shifting the transducer spectrum downward and lowering the transmission frequency, will decrease attenuation within the body and improve beam uniformity.

System changes such as transmit apodization, (a technique which extends the uniformity of the transmitted field) and compensation for transducer rolloff with angle can be made.

Another factor making transmit uniformity more challenging is the attenuation from the injected contrast agent. More sensitive detection techniques require a lower contrast agent concentration. A lower concentration decreases attenuation from the agent and therefore improves the uniformity of the transmit field. Techniques requiring less agent will be more robust for quantification. A final area of improvement is in the contrast agent. Contrast agents with improved Scattering-To-Attenuation-Ratios will be best for quantification.

Reference: Wei et al, Quantification of Myocardial Blood Flow With Ultrasound-Induced Destruction of Microbubbles Administered as a Constant Venous Infusion. Circulation. 1998;97:473-483.

SIMULATION OF NON-LINEAR GAS BUBBLE SCATTERING

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Simulations of the non-linear radius oscillations of gas bubbles encapsulated in shells are done. A set of ordinary differential equations for the bubble radius oscillation is used. The bubbles are surrounded by compressible fluid, thus linear propagation of the scattered wave is accounted.

Results: Let f_i be the incident and f_{res} the bubble resonance frequency. For $f_i < f_{res}/5$ the main non-linear effect is produced by the gas and shell non-linearity. A saturation of the positive amplitude of the scattered pressure, p_s, is produced in the positive period of the incident pressure, p_i.
When f_i approaches f_{res} from below, an attenuated resonance oscillation is introduced at the start of the pressure saturation. This oscillation has frequency close to f_{res} for a compressed bubble. The attenuation is given by viscous and radiation losses.
The spectrum of the oscillation determines the higher frequency generation in the non-linear scattering. When p_i contains many oscillations of similar amplitude, each positive pressure swing produces one such dampened oscillation, which gives a periodic form of p_s. This breaks the spectrum of p_s into harmonic bands of f_i .

The harmonic banding of p_s hence depends on the length of p_i. With short pulses, harmonic generation also depends on the polarity of p_i, and the technique of pulse inversion to remove odd harmonic bands in the scattered wave, is no longer complete.

As f_i passes above f_{res}, the excitation of the resonant oscillation diminishes, and the non-linear scattering of the bubble is reduced.

As f_{res} is determined at the elevated bubble saturation pressure, it increases with the positive amplitude of p_i , which increases the bandwidth of p_s. Using f_i slightly above f_{res} at low p_i, one can make f_{res} pass above f_i by increasing the positive amplitude of p_i, hence dramatically increasing the non-linear scattering.

LATE PHASE LIVER UPTAKE OF LEVOVIST – WHAT IS IT'S CAUSE?

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The phenomenon of late phase liver imaging using stimulated acoustic emission (SAEM) effects of Levovist® (Schering AG, Berlin, Germany) has been reported by abdominal ultrasound examinations. Against the background of very sensitive imaging techniques of modern ultrasound equipment (pulse inversion / wideband harmonics) this effect is successfully used for the detection of focal liver lesions. The purpose of this study was to evaluate the underlying mechanism of this phenomenon.

Using an established animal model harmonic color Doppler (ATL-UM9, L10-5) was used to investigate late phase liver imaging in 18 rats (Shoe:WIST SPF) 15 min after application of Levovist. One group of rats was pre-treated in order to block the reticulo-endothelial-system (RES). Video tapes of all scans were reviewed by independent readers. Furthermore, histological examination was performed by using cryo-cutting techniques combined with fluorescence microscopic analysis. Therefore fluorescence labeled Levovist was prepared and applied in pre-treated and untreated rats as well.

In the harmonic color Doppler evaluation a clear difference between untreated and pre-treated rats was seen regarding intensity and duration of SAEM effects. In untreated rats the SAEM effects were shown to be stronger and also longer-lived. The fluorescence microscopic analysis showed that, similar to fluorescent model particles in preliminary investigations, the distribution of fluorescence labeled Levovist within the liver parenchyma was also different between pre-treated and untreated rats. While in untreated rats fluorescence was predominantly seen in the periportal region where macrophages of the liver (Kupffer stellate cells) are located, a more diffuse distribution within the parenchyma of the liver was observed in the pre-treated rats.

The results of this indirect method show that the phenomenon of late phase liver imaging with Levovist is related to the function of the RES. As SAEM effects of Levovist also occur after blocking of the RES, other mechanisms like slowly moving microbubbles in the liver sinusoids or attachment to sinusoidal licking are likely to be involved.

QUANTIFICATION OF THE ACOUSTIC BACKSCATTER POWER AT 30MHZ FROM TWO FLUOROCARBON-FILLED ULTRASONIC CONTRAST AGENTS

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Introduction: Ultrasonic contrast agent solutions are composed of approximately 10^8 gas-encapsulated microbubbles/ml of solution. These microbubbles are of a size (<5microns) and composition such that when insonated at routinely used diagnostic frequencies (2-7MHz), the bubbles resonate and strongly scatter ultrasound. More recently there has been increasing interest in imaging and manipulating these contrast agent microbubbles at significantly higher frequencies for possible applications in targeting and delivering microbubble-encapsulated drugs to specific sites in the body. However the ultrasonic scattering properties of microbubbles at these frequencies are not well documented.

Aims: The aim of this study is to quantify the acoustic backscatter properties at 30MHz of two fluorocarbon-filled ultrasonic contrast agents at various concentrations using a modified intravascular scanner (HP Sonos).

Methods: The contrast agents were diluted to various concentrations using saline as the dilutant. The intravascular probe was inserted into the solution. One frame of unprocessed data was acquired at each concentration. The data was downloaded onto a PC. A region-of-interest of 128 data points and 9 ultrasonic lines wide was chosen. Over these region-of-interests, mean backscatter power was calculated and referenced to data collected from a standard reflector.

Agent	Type of Agent	Capsule	Encapsulated Gas	Bubble Size	Concentrations Studied (Microbubbles/ml)
DEFINITY (DMP-115)	Encapsulated Bubble	Lipid	Perfluoropropane	mean 2.5μm	$100 \times 10^6 \rightarrow 0.009 \times 10^6$
OPTISON	Encapsulated microsphere	Albumin	Octafluoropropane	mean 3.7μm	$50 \times 10^6 \rightarrow 0.019 \times 10^6$

Results : At a depth of 2mm, both agents gave maximal backscatter values at concentrations between 5-10 x 10^6 microbubbles/ml. For concentrations greater than these, the ultrasonic signal was strongly attenuated by the contrast agent. At concentrations as low as 0.039 x 10^6 microbubbles/ml, the mean backscatter level from both agents was at least 10dB greater than the signal from saline.

Conclusions: This study illustrates that at concentrations as low as 0.039 x 10^6 microbubbles/ml corresponding to less than 15 microbubbles per sample volume, measurable backscatter can be detected. Such contrast agent microbubbles may therefore be of use in targeting and drug delivery at specific sites within the arteries.

VALIDATION OF CONTRAST ECHOCARDIOGRAPHY: QUANTITATIVE MYOCARDIAL BLOOD FLOW AND VOLUME MEASUREMENTS USING MICROSPHERES (FLOW) AND RADIO-LABELED RED BLOOD CELLS AND PLASMA (VOLUME)

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Background: In vivo and in vitro calibration of a contrast agent (Optison™) to a receiver (Power Doppler Harmonics) previously demonstrated a direct, monotonic relationship.

Purpose: To validate microvascular blood volume and flow in normal and infarcted myocardium with contrast ultrasound using the "gold standards" of microspheres (flow) and radiolabeled blood cells Cr-51 and plasma Fe-59 (volume).

Methods: Five dogs underwent anesthesia and open chest preparation. A continuous infusion of Optison™ was administered using Power Doppler Harmonics and the multiple isotope labeling technique.

Results: A statistically significant difference was observed between the normal and infarcted zones by all three methods ($p<0.001$): 1.Videointensity by contrast echo, 2.Blood flow by microspheres, and 3. Blood volume by RBC's and plasma.

Dog #	Blood Flow (Microspheres)	Blood Volume (Radiolabels)	Contrast Echo	
infarction	*% change from RV control*	*% change from RV control*	*signal value*	*% change*
#1 none**	1.022 ml/min/g	6.456% total volume	202,9	N/A
#2 (pre-)	3,24%	4,60%	112,1	
(post-)	-75,7%	-30,6%	44,5	-60,3%
#3 (pre-)	1,35%	-1,20%	174	
(post-)	-76,3%	-60,7%	4,38	-97,5%
#4 (pre-)	4,25%	16,80	164,5	
(post-)	-63,7%	-29,0%	12,2	-92,6%
#5 (pre-)	1,30%	0,44%	147,0	
(post-)	-91,6%	-31,8%	16,2	-89,0%
Mean	**-76,8%**	**-38,0%**		**-84,9%**
SD	11,4	15,2		16,7

**LV tissue only

Conclusion: Contrast echocardiography is a valid technique for assessing blood flow and volume based upon a statistically significant response between ultrasound signal intensity and established microvascular reference standards [Cr-51 labeled RBC's and Fe-59 labeled plasma and latex microspheres].

OPTICAL IMAGING OF CONTRAST AGENT MICROBUBBLES IN AN ULTRASOUND FIELD WITH A 100 MHZ CAMERA

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Ultrasound contrast agents, used in the field of medical diagnosis, contain small microbubbles of a mean diameter of about 3 μm. The acoustic behavior of these bubbles in an ultrasound field has been subject to many investigations. In this study, we propose a method to visualize the behavior of the bubbles in a 0.5 MHz ultrasound field under a microscope with a frame rate of 4 MHz. The contrast agent SonoVue™ (Bracco Research SA, Geneva, Switzerland) was used in the experiments. SonoVue™ consists of sulfur hexafluoride gas bubbles encapsulated by a flexible phospholipid shell having a mean diameter of 3 μm.

For low acoustic pressures (peak negative pressure of 0.12 MPa), the radius-time curve as measured from the optical images is in agreement with the theory. For higher acoustic pressures (peak negative pressure of 0.6 MPa), the recorded radius is significantly larger than predicted by theory and sudden change in the bubbles shape has been noticed.

The figure shows the 8 observations at the same acoustic pressure (P_ = 0.6 MPa, MI=0.85). Nevertheless, the recording of the images started at the beginning of the transmitted burst (see figure 1B, t1), i.e., the moment the ultrasound wave reached the ensemble of bubbles. In this experiment, the exposure time of the first 2 images was set to 500 ns, and the rest of the images were recorded with an exposure time of 250 ns. The total time span was therefore 2.5 μs. The first images show a minor change in diameter, however, the diameter increases dramatically in images 6,7 and 8. The course of the change of diameter of 2 bubbles is given in the figure. The initial diameter of bubble 'a' is 1 μm. It first decreases and then increases up to 7 μm. In this example, all the different bubbles show similar behaviour. The change in radius was underestimated by simulated results, which showed only an increase of 20-50% of the initial diameter.

Discussion and conclusions

During the exposure time (250 ns) the bubble continuously expands or contracts. Therefore, the motion of the bubble wall will be integrated and appears on the images as dark ring (blurring). This became clearly visible in the figures 3-5. Nevertheless, for the analysis the maximum diameter during

exposure was considered. In the simulation this effect has not been taken into account. The measured peak to peak amplitude of the transmitted burst was used as input for the simulation.

The contrast agent was freely flowing through a small tube during experiment. There was no need for fixation (e.g., with a pipette), which is necessary if stroboscopic investigation is considered, and therefore our set-up approaches the in-vivo situation. Flow was low and exposure time short, therefore bubble displacement during experiment was negligible as can be seen in all the images shown.

High frame rate recordings are essential for further development of the different areas in which contrast agents can be used. First, this includes the development of new detection methods. Some of the current methods are based on the change in scatter response of the bubble from successive pulses. For these methods, the exact response during insonification is of non-importance. The described optical observations show that the bubble diameter increases during insonfication and exceeds the values expected from theory [1]. This opens ways to interrogate the bubble differently and to use the acquired information directly without repeated interrogations. Also the optimal response as function of frequency and acoustic amplitude can be determined.

Secondly, acoustic characterisation always relates to a cloud of bubbles. The elasticity and the viscosity of the shell are derived from the acoustic measurements, and so they give only average values. Through real-time optical visualisation, the exact contribution of each bubble to the ultrasonic backscattered signal can be determined and consequently the elasticity and viscosity of the shell of each bubble. Statistics can be carried out as function of the diameter; new contrast agents can be rapidly evaluated and quality control is feasible.

A third aspect is drug delivery under guidance of ultrasound if a drug is included in the shell of the microsphere. Locally delivering the drugs under ultrasound irradiation has proven to be a new opportunity using contrast agent microspheres. With optical observation the exact mechanism behind the release can be studied.

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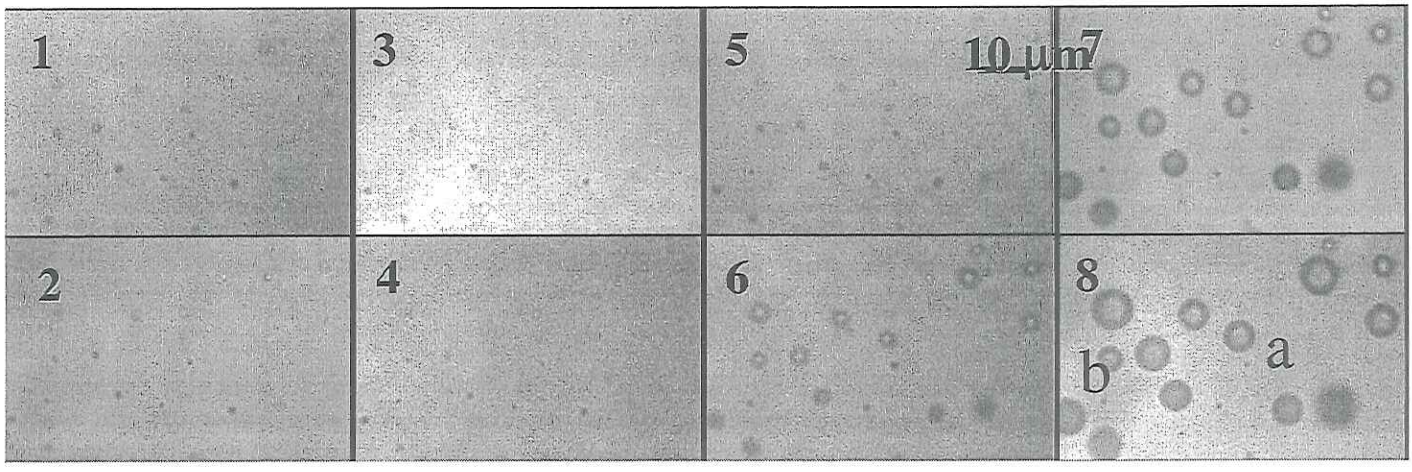
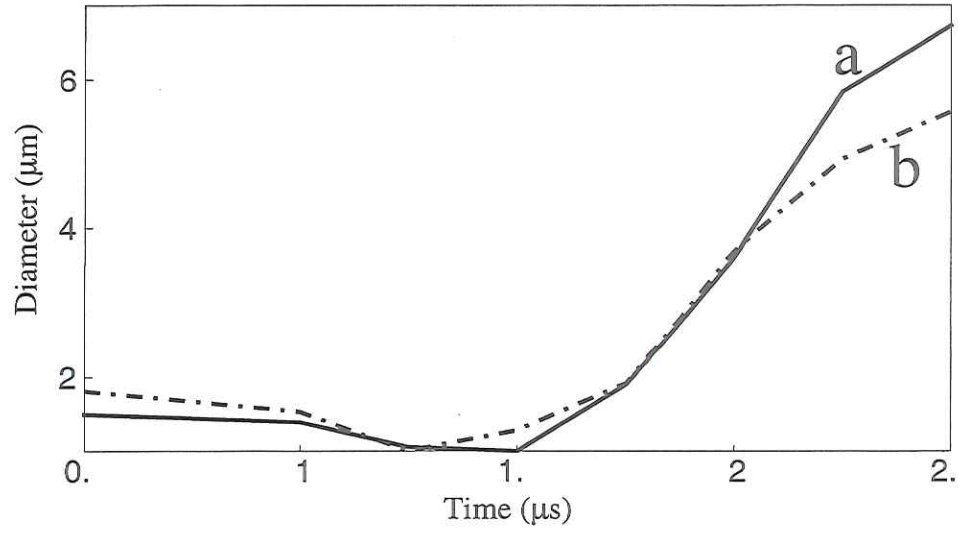

1
3
5
10 µm
7
2
4
6
8
b
a


a
b
Diameter (µm)
6
4
2
0.
1
1.
2
2.
Time (µs)

HARMONIC BEAM PROFILES FOR PHASED ARRAY TRANSDUCERS

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Ultrasound image quality has experienced a significant improvement over the past years with the utilization of harmonic frequencies. This brought the need to understand the physical processes involved in the propagation of finite amplitude sound beams, and the issues for redesigning and optimizing the phased array transducers. New arrays with higher imaging performances are essential for tissue imaging and contrast imaging as well.

In that context, a numerical algorithm is developed to solve the KZK wave propagation equation. The equation is solved in the time domain and the algorithm is based on finite differences with a stepping in the z direction. The algorithm uses the alternating direction implicit method to alternate the solution between the lateral directions, i.e., the integration over one z step is split into two half-steps, the first of which is implicit in x direction and explicit in y, and conversely for the second step. This method is unconditionally stable.

For sound sources that are symmetric both with respect to the x and the y axis (linear arrays), the equation needs to be solved in the quarter space $x \geq 0$, $y \geq 0$ only, and for reason of symmetry, the boundary condition $\partial P/\partial x = \partial P/\partial y = 0$ was applied when $x = y = 0$. To validate the algorithm, measurements and simulations were carried out on a 4.6 MHz square transducer. Comparison of the measured and the computed data showed good agreement for low and high excitation levels.

The former boundary conditions are not valid for phased array transducers. Thus, the algorithm was adapted to calculate the acoustic beam profile generated by phased array transducers. Using the adapted algorithm, a numerical simulation was performed on a phased array transducer containing 24 elements. Each of the elements was 0.2 mm in width and 12 mm in height, and operated at 3 MHz and at peak negative pressure of 0.2 MPa. The focus was adjusted to 50 mm, the pitch was 0.5 mm and the steering angle was set to 20 degrees. The simulation showed that the second harmonic beam is narrower than the fundamental with less energy in the near field. In addition, the grating lobes are significantly lower. The results are also compared to analytic solution using the linear wave propagation equation [1].

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THE EFFECTS OF THE BUBBLE SHELL ON SINGLE-PULSE NONLINEAR SCATTERING BY CONTRAST AGENTS

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In a previous paper, we demonstrated only partial success at the experimental verification of a theoretical model of nonlinear scattering by free air bubbles, even when the heterogenicity of bubble size and local incident amplitude is taken into account. Three aspects of discrapency were revealed: the model overestimates the harmonic ($2f_0$) component in the echoes; the model does not demonstrated an increase in both fundamental (f_0) and $2f_0$ scattering coefficients at high incident powers; and the model underestimates the amount of spectral broadening ($1.5f_0$) at low powers. Based on theoretical considerations and numerical experiments, we hypothesized that the properties of the shell play the most important role: the presence of the shell dampens the $2f_0$ oscillation; the disruption of the shell at high powers leads to increased scattering; and the heterogenicity of shell thickness leads to a subpopulation of bubbles being disrupted at low powers, emitting the $1.5f_0$ signals.

To test this, f_0, $2f_0$ and $1.5f_0$ scattering coefficients were measured as functions of both incident power as well as the exposure history of the bubbles. Diluted contrast agents flowing in a sample cell were exposed to two ultrasound pulses. The power of the first was varied from 30kPa to 3MPa but that of the second was constant at 240kPa. This reference pulse probes the effect of the first pulse power on the shell, and was transmitted after a very short delay (15 microsec), so the influence of bubble gas solubility and diffusivity was minimized.

Results from Sonovist (Schering, Berlin), Definity (DuPont, Billerica, MA) and Optison (Mallinckrodt, St. Louis, MI) were compared to reveal dependence on shell types.

It was found that $2f_0$ scattering decrease with increased shell stiffness. Significantly increased scattering coefficients (10-40dB) at high power was found in Sonovist and was associated with more than 20dB changes in reference scattering. The presence of spectral broadening was also shown to associate with the disruption characteristics of the agent. These results support the significant of shell effect in single pulse nonlinear scattering by contrast bubbles.

INITIAL EXPERIENCE WITH MULTI-PULSE RELEASE IMAGING

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Currently available contrast agents for diagnostic ultrasound imaging consist of encapsulated gas bubbles. When subjected to low power ultrasonic pulses, the scattering properties of the bubbles remain unchanged. At high power insonation, the encapsulating shell of the bubbles can be broken, and the gas will be released. As free gas bubbles emerge and diffuse into the blood, a transient increase in backscatter occurs [1]. Also, the transient disappearance of the bubbles results in random changes in backscatter from pulse to pulse.

Existing harmonic power-Doppler methods use multiple destructive pulses to obtain a single image. From observations of bubble behaviour, it seems that a single high power pulse is sufficient to destroy or modify the bubbles, and a new method using a single destructive pulse and multiple non-destructive pulses has been proposed [2]. In the proposed setting, the method will work by first transmitting several low power pulses to obtain a high-resolution reference image without changing the contrast agent. By using several pulses, tissue motion can be estimated and predicted. A high power burst is then transmitted to uniformly destroy bubbles along the line of sight, and release free gas bubbles. Finally, several more detection pulses are transmitted and used to detect the changes introduced by the burst. The idea behind the method is to separate destruction and detection, and thereby reduce the need to use long destructive pulses for contrast imaging. Using shorter pulses will improve the spatial resolution of the image, while the separate high power burst used to release free gas bubbles ensures sufficient sensitivity for bubble detection. Lower power for the detection pulses will also reduce the contribution to the harmonic frequency band caused by non-linear propagation, and will thereby enhance the harmonic signals from non-linear bubble oscillations relative to harmonic signals from tissue.

The previously presented results with the method [2,3] have been single line acquisitions taken from preliminary *in vitro* experiments with separate transducers for transmitting the detection pulses and the release burst. In order to investigate the feasibility of the method for clinical use, a System Five ultrasound scanner (GE Vingmed Ultrasound, Horten, Norway) has been programmed to transmit pulse sequences using a standard phased array transducer. The pulse sequence consists of a variable number of pulses, which are repeated for each beam direction in the image. The pulse frequencies, lengths and amplitudes can be specified individually for each pulse in the sequence. Real-time

processing and display was not included in the first implementation. Instead, Radio Frequency data from all the pulses were recorded and processed off-line using Matlab (The Mathworks Inc, Natick, MA). A special filter using polynomial prediction [3] was used to remove clutter signals. The intensity of the remaining contrast signal was coded in colour and combined with the background greyscale image, like in colour Doppler imaging.

The modified system has enabled full sector scans with the new method. Initial experiments were performed using a capillary flow phantom with simulated tissue motion to establish reasonable settings for the involved parameters. Based on these settings, a few *in vivo* experiments have been performed in animals and patients.

The results from this limited number of experiments show that the release approach works for ultrasound contrast imaging, and the method has been implemented on existing ultrasound equipment without hardware modifications. To compare the performance of release imaging relative to other techniques, such as harmonic power Doppler and pulse inversion Doppler methods, further experiments are needed.

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OPTIMIZATION OF SOFTWARE AND HARDWARE FOR THE DETECTION OF ULTRASONIC CONTRAST AGENTS

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The efficacy of contrast agents for clinical diagnostic is critically dependent not only on bubble properties, but also on ultrasound system parameters and functionality. Contrast agents have developed through several generations providing longer in-vivo survival times for imaging. Similarly, ultrasound systems are challenged by the extra demands of contrast agent imaging over and above that of conventional non-contrast imaging.

The challenges extend to all components of the system including the transducer, transmit and receive circuitry, and digital signal processing circuitry.

Additional nonlinear frequencies contributed by the contrast agent bubbles to the received echoes increase the bandwidth of the returned signal, requiring that transducer and receiver bandwidths be wide enough to capture the additional information. The transmit pulser must be highly flexible to implement a variety of pulse sequences to take advantage of bubble properties. For advanced pulse sequences such as phase inversion, a high degree of symmetry is required between the zero degree and 180 degree analog pulses for cancellation of the linear signal components. Digital processing techniques such as pulse addition and subtraction may be applied to the received pulse sequences. New opportunities in quantitation are possible with contrast agents. For example, time intensity curves may be obtained from regions of interest in the tissue. The design of the entire ultrasound system is affected by the requirements of contrast agent imaging.

EXPERIMENTAL OBSERVATIONS OF THE SENSITIVITY AND FREQUENCY RESPONSE OF THE POWER MODULATION TECHNIQUE FOR CONTRAST IMAGING

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Agilent Technologies, Inc.

A multi-pulse technique for imaging with improved sensitivity to microbubble contrast agents is investigated. In this technique, referred to as Power Modulation, the transmit amplitude of insonifying pulses is changed. This transmit amplitude change induces changes in the response of contrast agent. On receive, corresponding gain adjustments are made to the received lines of data, which are subsequently subtracted. Most of the linear responses are thereby cancelled, and what remains is dominated by signals from the microbubbles.

The sensitivity and frequency response of this new imaging technique are explored in vitro using a tissue phantom and Optison ™, MBI, Mallinckrodt contrast agent. The sensitivity of the technique is expressed as the ratio of contrast agent to tissue signal levels in decibels. Of principal interest is that the strongest response of the contrast agent occurs at or near the fundamental frequency of the transmit acoustic waveform.

The sensitivity and frequency response of the technique is evaluated at high and low power levels, as well as for transmit waveforms having relatively narrow and wide frequency bandwidth.

MYOCARDIAL FLOW AND VOLUME QUANTIFICATION WITH POWER PULSE INVERSION AND FLASH CONTRAST IMAGING

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Imaging of contrast agents using a low mechanical index modality such as Power Pulse Inversion allows visualization of myocardial perfusion in real-time with minimal microbubble destruction. However, the initial "wash-in" of microbubbles into the myocardial microvasculature is heavily dependent on several factors including the method of contrast administration (e.g. bolus injection or continuous infusion), the saline flush volume and injection technique. Therefore, although qualitative differences in the way which myocardial beds perfuse may be noted during this initial wash-in phase, quantification of flow is not possible.

The current technique for a contrast perfusion exam requires intermittent triggered imaging at a high mechanical index (MI). This method captures a "snapshot" (single frame) of contrast enhancement at a particular time in the cardiac cycle. For each frame acquired the contrast intensity is captured, but as a consequence of the high acoustic amplitude signal transmitted (typically, MI > 0.8), the contrast agent in the imaging plane is simultaneously destroyed. (Wei, et al; 1997) Multiple "snapshots" at different triggering intervals are acquired, and the contrast intensity is plotted as a function of replenishment time (the amount of time between images). This data has been shown to fit a 1-exponential curve ($A(1- \exp(-\beta t))$), from which parameters of flow and volume may be easily extracted. (Wei, et al, 1998) Unfortunately, the time required to collect enough images for analysis can be more than 1 minute, precluding the method from use in some types of cardiac stress examinations. Also, most ultrasound equipment must suspend imaging between the "snapshots" in order to preserve microbubbles from being destroyed by the real-time high MI acoustic environment. Therefore, the sonographer/technician must maintain the scanplane without real-time image feedback.

Flash Contrast Imaging is a key component of real-time perfusion imaging using Power Pulse Inversion. Flash imaging allows the user to transmit n frames (n = 1,2,3...) at a high mechanical index (hence the "flash") during low MI real-time perfusion imaging. The high MI frames may be transmitted at any time (manual pushbutton), or triggered at a specific part of the cardiac cycle. Immediately after the high MI frames are transmitted, the system returns to low MI real-time imaging so that the replenishment of myocardial contrast can be visualized in real-time. The advantages of Flash Contrast Imaging are: 1) the user can precisely regulate the time of contrast destruction, typically at the point when the myocardium is fully perfused with agent; 2) the contrast intensity at

every point in the cardiac cycle can be captured in real-time; and 3) imaging is real-time, allowing the technician to easily maintain the proper echo window and scanplane. If a continuous infusion of contrast agent is administered, the flash frames can be transmitted repeatedly during or after myocardial replenishment. This allows the clinician to assess multiple echocardiographic views without repeat injections or switching between triggered and real-time high MI modes, which conserves time and contrast agent.

Off-line analysis software such as HDILab can be used to quantify myocardial flow and volume after intermittent triggered imaging or Flash Contrast Imaging. Figure 1 illustrates a replenishment curve generated using high MI Power Harmonic Imaging. Two data points were collected at 7 different pulsing intervals. The 14 data points required just over one minute of acquisition time with imaging suspended between the acquired frames. Also, since grayscale methods generally have a tissue harmonic background level and Power Harmonics have a background motion component, background subtraction post-processing must be performed before curve fitting. (Tiemann, et al) Quantification with Flash Contrast Imaging is significantly faster, and since the method is real-time, captures data points from the entire cardiac cycle. The process of "flash" and replenishment is illustrated in Figure 2 and data from both a normal and hypoperfused myocardial bed is shown in Figure 3. Each curve in Figure 3 has 85 data points and took only 9 seconds to acquire.

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Tiemann K, Becher H, Köster J, Schlosser T, Pohl C. (1998) Quantification of Tissue Perfusion by Means of Bubble Destruction Using Harmonic Power Doppler Imaging. Circulation, 98(17):I 570.

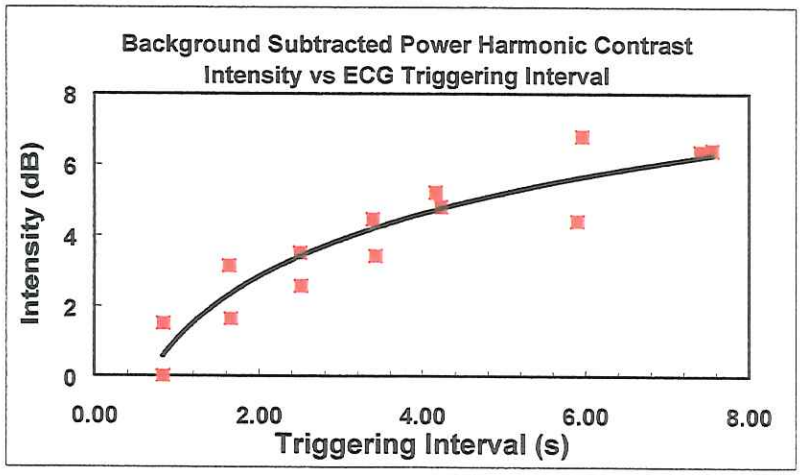

Figure 1: In the method for quantification of myocardial perfusion proposed by Wei et al., a curve is generated by high MI triggering at multiple ECG intervals. A plot of contrast intensity at 1, 2, 3,... ECG intervals between triggered images are then fit to a monotonically increasing exponential function. The initial slope of this curve is related to the bulk myocardial blood flow velocity, and the plateau value reflects the blood volume. In this example, 14 data points (images) are acquired in just over one minute.

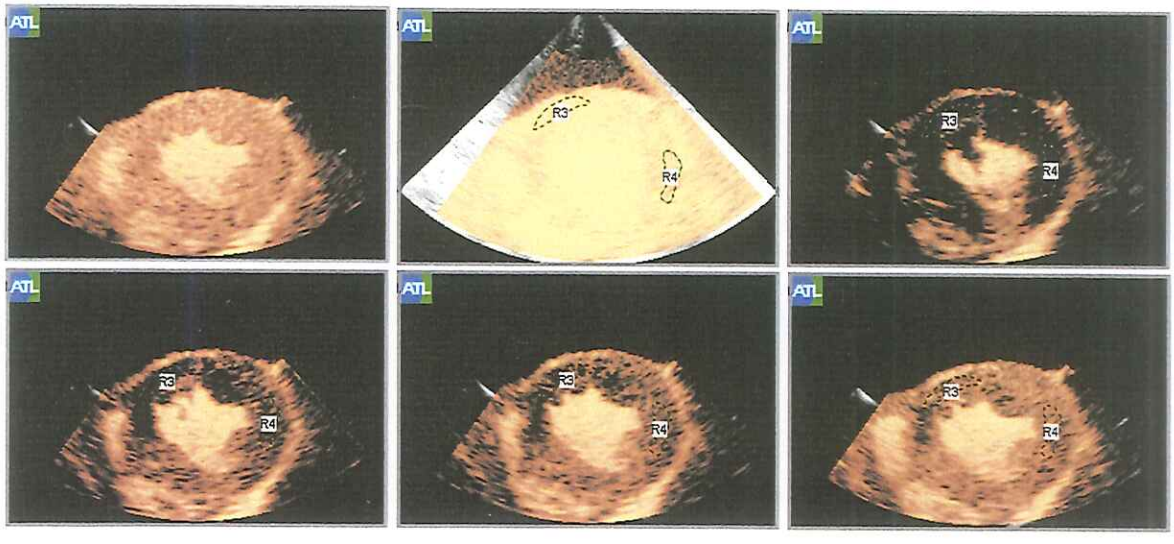

Figure 2: Flash Contrast Imaging with Power Pulse Inversion. At the point of complete myocardial perfusion (top row left), a "flash" frame is triggered (top row center). Contrast is destroyed in myocardium but not cavity (top row right). Myocardial replenishment of contrast occurs over several cardiac cycles and can be seen visually (lower row).

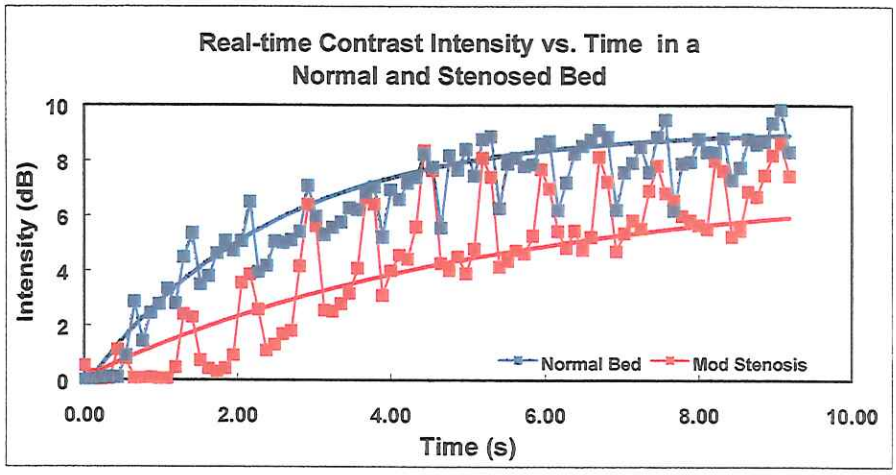

Figure 3: Power Pulse Inversion at a low MI (MI = 0.15) allows the visualization and collection of contrast replenishment data in real-time. This data was collected after a single high power Flash frame (MI = 1.3) was used to destroy all contrast agent in the myocardium. Replenishment of contrast was recorded for about 9 seconds. The normal bed replenishes in about 5 seconds, as evidenced by the plateau. The bed with a moderate stenosis (approx. 80%) has a much slower replenishment rate, and does not reach plateau in the time allotted. Curves of the form $(A(1- \exp(-\beta t)))$ can be fit to the data by the method of Wei, et. al.

CAVITATION OF INSONIFIED MICROBUBBLES: GENERATING SOUND AND HEAT

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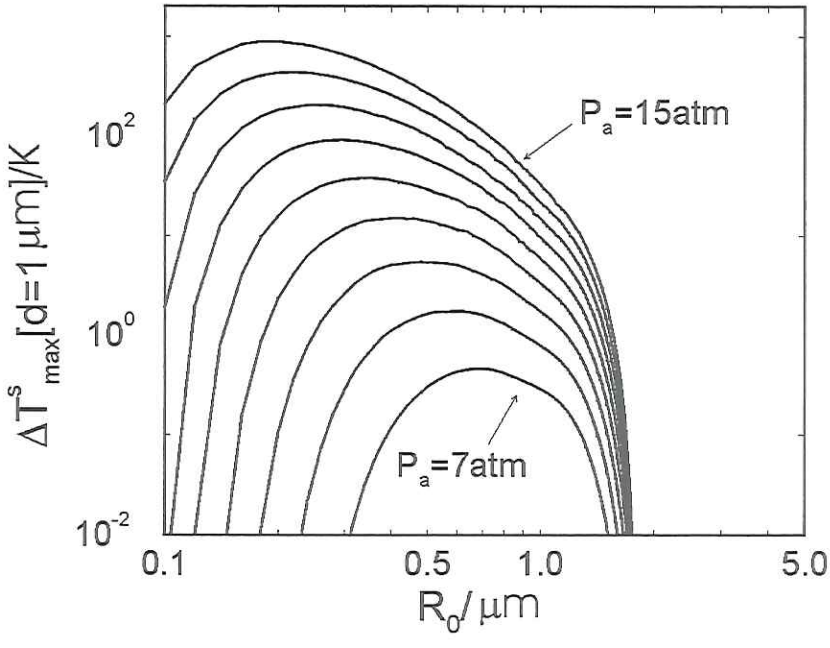
This theoretical study focuses on the dynamics of strongly driven microbubbles in ultrasound contrast agents and its consequences for diagnostic applications. The highly nonlinear response of the bubbles to the driving sound can be beneficial to diagnostics. Nonlinear scattering cross sections, e.g., are greatly enhanced compared with linearresponse theory. Moreover, nonlinear features of the spectra of emitted sound (such as emission at harmonic frequencies) can be exploited for better imaging contrast. However, the characteristics of sound emission depend sensitively on bubble size distribution and driving pressure, which makesharmonic imaging difficult. Ultraharmonic frequencies are found to be morerobust for yielding enhanced contrast. Too strong driving is inefficientbecause much of the energy of the bubble collapse is deposited in high frequency acoustic waves, which are undetectable by diagnostic devices.

The high frequency sound is absorbed strongly in the blood and tissue ans leads to pronounced localized heating around the bubbles (at distances of a few micrometers, see figure), thus creating a potential thermal risk in clinical applications when very strong driving pressure amplitudes are used.



Maximum temperature rises observed at a distance of 1 μm from the center of a collapsed bubble, as a function of bubble rest radius R_0 and effective driving pressure amplitude P_a. For R_0 near resonance and the highest P_a= 10 atm, ΔT^s_{max} reaches several 100 K in a very small volume and for very short times.

INTRAVENOUS ANTISENSE ADMINISTERED BOUND TO PERFLUOROCARBON EXPOSED SONICATED DEXTROSE ALBUMIN MICROBUBBLES INHIBITS STENOSIS FORMATION FOLLOWING CORONARY BALLOON INJURY

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Intravenous (IV) perfluorocarbon exposed sonicated dextrose albumin (PESDA) microbubbles and therapeutic ultrasound (TUS) have enhanced the delivery of antisense (AS) to vascular targets. The purpose of this project was to determine whether PESDA-mediated delivery of IV AS to the protooncogence c-myc could prevent stenosis formation following coronary balloon injury (BI) in the left anterior descending (LAD) or left circumflex (LCX) arteries. Thirty-seven consecutive pigs underwent coronary BI followed by randomization to either a) IV AS and TUS alone (AS US), b) AS and PESDA alone (PAS alone), c) AS/PESDA + TUS, d) reverse sequence (Sense/PESDA) + TUS (Sense US), or e) control. TUS (1 megahertz; 1 watts/cm2) was given for either 30 seconds (PAS US 30 sec) or 3 minutes (PAS US 3 min) following IV injection of AS/PESDA. At 4 weeks, intravascular ultrasound (IVUS) and histologic measurements of intimal area (IA), thickness (MIT), and % area stenosis (%AS) were made. Results. AS/PESDA alone resulted in both significant lower %AS (LAD) and MIT (LCX) (*p<0.05; ANOVA). The degree of inhibition achieved with AS/PESDA was no longer evident when TUS was added (Table). Conclusion: IV PESDA, without TUS, may be a non-invasive method of delivering AS to the coronary artery, and thus preventing restenosis following BI. The mechanism may be microbubble adherence to injured endothelium or perfluorocarbon-increased endothelial permeability.

	Intimal Area (mm^2)		MIT (mm)		% Area Stenosis	
	LAD	LCX	LAD	LCX	LAD	LCX
PAS alone	0.08	0.13	0.13	0.10*	16±7**	30±19
PAS US 30 sec	0.22	0.33	0.22	0.34	28±12	43±13
PAS US 3 min	0.14	0.38	0.16	0.22	19±5	32±18
AS US	0.16	0.30	0.17	0.23	20±6	31±16
Sense US	0.21	0.44	0.22	0.33	23±9	33±13
Control	0.45	0.21	0.29	0.19	28±7	26±3

*p<0.05 compared to all other groups; **p<0.05 compared to control

ENDOTHELIAL DYSFUNCTION AND THE DEVELOPMENT OF ATHEROSCLEROSIS

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The endothelial surface actively plays multiple, critical roles in maintaining vascular physiology. The occurrence of abnormal endothelial function is a critical early event in the development of atherosclerosis, and predates the angiographic and ischemic manifestations of coronary artery disease.

Abnormal leukocyte adherence to the arterial wall endothelium is one of the initial cellular events in the development of atherosclerosis and is mediated by specific leukocyte adhesion molecules on the surface of endothelial cells. These adhesion molecules, including intercellular adhesion molecule-1 (ICAM-1), E-selectin, and vascular cell adhesion molecule-1 (VCAM -1) are focally expressed on arterial endothelium overlying early atherosclerotic lesions and are upregulated in the setting of coronary risk factors.

Methods to evaluate endothelial function

Methods for studying endothelial function *in vivo* have limitations. Absence of the expected vasodilator response to acetylcholine requires coronary catheterization and angiography. Non-invasive assessment of endothelial-dependent flow-mediated vasodilatation has been performed using measures of brachial artery diameter during reactive hyperemia, which is an indirect approximation of coronary endothelial function, and limited in image resolution.

Microbubble-endothelial interactions as a basis for studying endothelial function

Interactions between the endothelial cell surface and microbubbles used in myocardial contrast echocardiography (MCE) may form a basis for studying endothelial biology. Under normal conditions, sonicated albumin microbubbles (Albunex) mimic the intravascular behavior of red blood cells in the beating heart and do not adhere to the vascular lining. However, during pathophysiologic states associated with endothelial disruption (e.g. ischemia, cardioplegia infusion), microbubble and red cell transit rates become uncoupled, such that the microbubble transit time is prolonged.

Delayed microbubble transit through the coronary microcirculation may be due to microbubble adhesion to endothelial cells in the setting of endothelial dysfunction. If such is the case, the study of microbubble interactions with endothelium could: (1) form the basis for non-invasively detecting coronary microvascular endothelial dysfunction *in vivo*; and (2) provide an approach to the specific

interrogation of endothelial cell phenotype (e.g. identification of surface adhesion molecule expression) using custom-designed microbubble agents uniquely targeted to distinct cell surface markers.

Based on these considerations, studies have been performed to further investigate the nature of microbubble adhesion to endothelial cells. Using perfused cultured human coronary artery endothelial cells, we have recently shown that Albunex adheres to exposed extracellular matrix of denuded endothelial surfaces, and that microbubble adhesion to the matrix is enhanced in the setting of endothelial activation. Using a similar model of perfused cultured endothelial cells, we have also shown that Albunex sticks to cardioplegia-perfused endothelial cells, but not to endothelial cells perfused with culture medium.

We have recently attempted to develop an approach to the *in vivo* identification of leukocyte adhesion molecules using contrast echo agents (Figure 1). A perfluorocarbon gas-filled microbubble targeted to bind to intercellular adhesion molecule-1 (ICAM-1) has been designed by incorporating anti-ICAM-1 antibody on the bubble shell. We have shown that non-targeted microbubbles (non-specific IgG-conjugated) do not adhere to normal (Panel A) or interleukin-1B (IL-1B)-activated (Panel B) cultured human coronary artery endothelial cells, whereas anti-ICAM-1 labeled microbubbles stick to IL-1B activated endothelial cells overexpressing ICAM-1 (Panels D and E). These findings set the stage for the characterization of endothelial function using contrast ultrasound.

Summary

Abnormalities in the structure and function of the endothelium mediate the early pathogenesis of atherosclerotic lesions. The pathophysiologic consequences of endothelial dysfunction include abnormalities in coronary perfusion which ultimately result in the ischemic symptoms of atherosclerotic cardiovascular disease. Methods of assessing the integrity of the coronary endothelium *in vivo* are either invasive, relatively non-specific, or limited by spatial resolution. Myocardial contrast echocardiography may offer a non-invasive method to investigate the structural integrity of the endothelium, and a unique tool to study specific features of endothelial cell phenotype in the microcirculation.

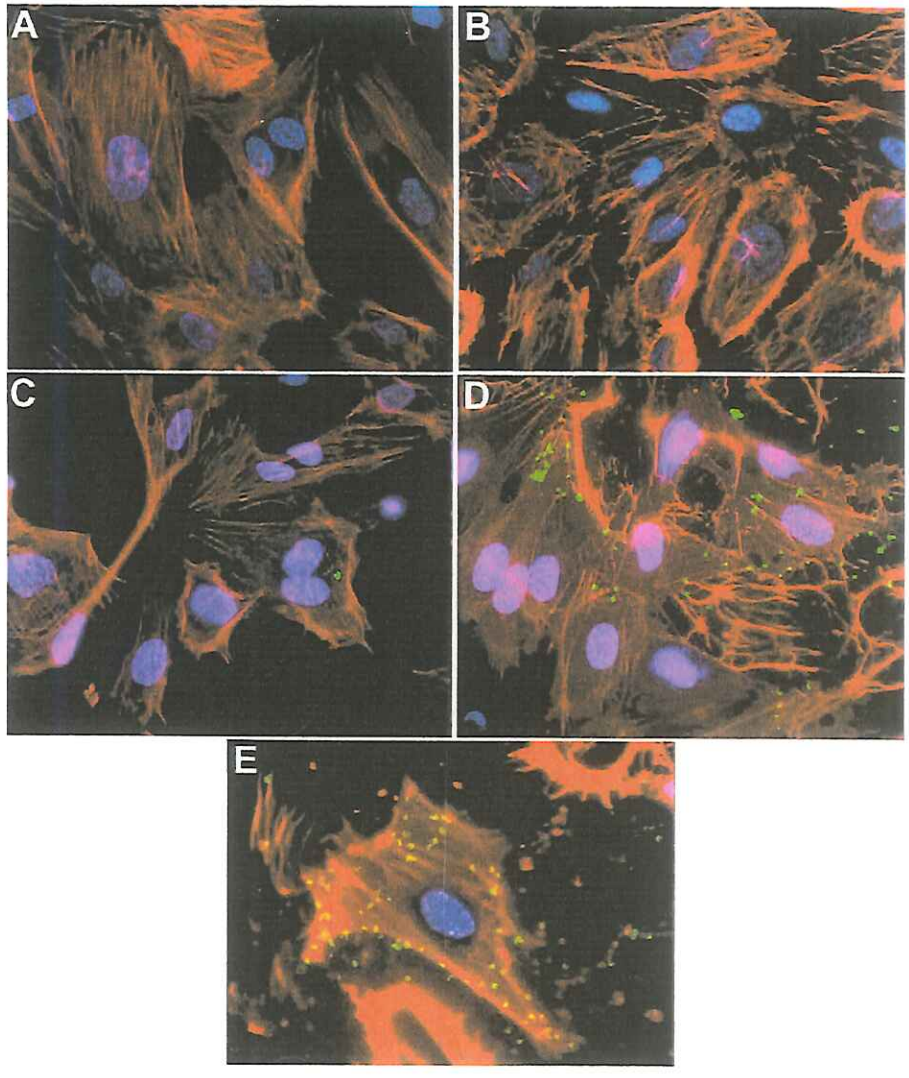

Figure 1:

Photomicrographs of rhodamine phalloidin-stained cultured human coronary artery endothelial cells (red fluorescence) exposed to fluorescein-labeled microbubbles (green fluorescence) during different states of endothelial activation induced by interleukin-1β. Nuclei are stained blue (Hoechst stain). Panel A: Normal cells exposed to non-specific IgG conjugated bubbles; Panel B: Activated cells exposed to IgG conjugated bubbles; Panel C: Normal cells exposed to anti-ICAM1 conjugated bubbles; Panel D: Activated cells exposed to anti-ICAM1 conjugated bubbles; Panel E: One activated cell with multiple adherent anti-ICAM1 conjugated bubbles.

NON-INVASIVE IMAGING OF INFLAMMATION WITH CONTRAST-ENHANCED ULTRASOUND

Jonathan R. Lindner

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The microvascular endothelium plays a key role in regulating normal leukocyte trafficking and mediating inflammatory responses. These inflammatory processes play a major role in the pathophysiology of many cardiac disorders including ischemia-reperfusion injury, myocarditis, and transplant rejection. An adequate method to assess microvascular inflammatory alterations is not currently evaluable. We have recently described persistent tissue opacicifiation during myocardial contrast echocardiography in regions of injury and inflammation. This finding suggests that albumin microbubbles are retained within injured/inflamed tissue. Accordingly we performed intravital microscopy of the cremaster muscle of mice during simultaneous intravenous injections of fluorescein-labeled albumin and lipid microbubbles. Under normal conditions, microbubbles passed through the microcirculation unimpeded. After ischemia-reperfusion injury or during TNF-α-mediated inflamation, both albumin and lipid microbubbles were retained within venules via their attachment to leukocytes adherent to the venular endothelium. The number of microbubbles that persisted correlated well with the extent of inflammation. Flow cytometry was used to determine the mechanism of microbubble attachment to activated leukocytes. Albumin microbubble binding to leukocytes was mediated by the leukocyte β_2-integrin Mac-1 while lipid microbubble binding was mediated by serum complement deposited on the microbubble surface which served as a ligand for leukocyte complement receptors. Light microscopy also demonstrated that these microbubbles are phagocytosed and remain intact intracellularly for at least 15 min. These microbubbles retained their acoustic activity, indicated by their gas volume reductions during repetitive single pulses of ultrasound at high pressures. We conclude that contrast-enhanced ultrasound has the potential to assess inflammation in organs accessible by ultrasound imaging.

QUANTITATIVE EVALUATION OF NEOANGIOGENESIS IN A RAT SPONGE MODEL USING SONOVUE™

A. Broillet, R. Ventrone, A.Hiver, X. Fouillet, A. Nunn, M. Schneider

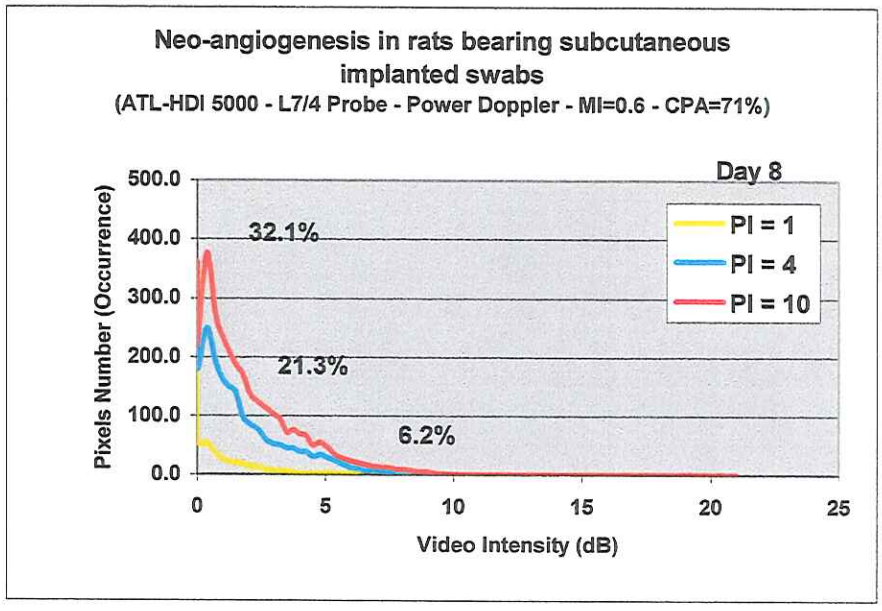
Bracco Reasearch S.A., Geneva, Switzerland

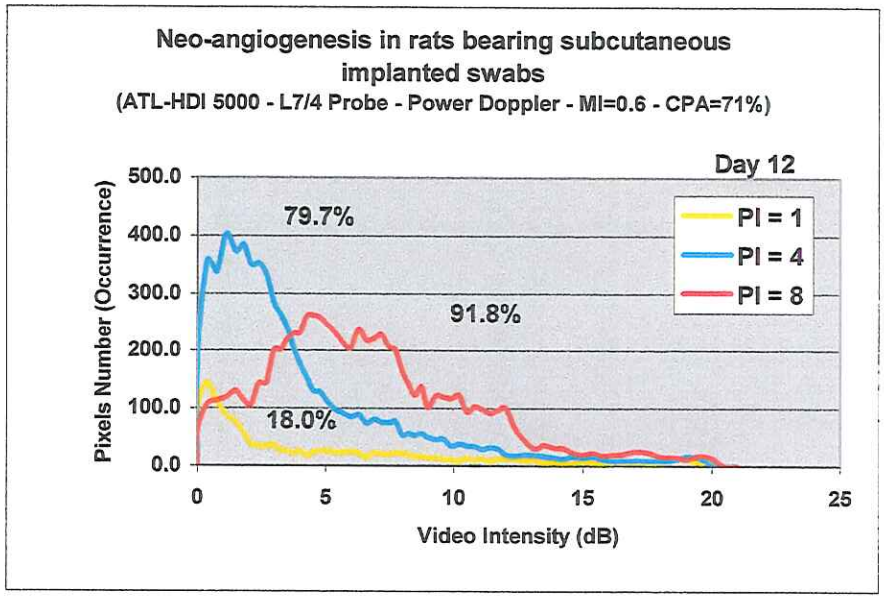
Angiogenesis is a key stage in the cell proliferation process and particularly in the development of malignant tumors. Clinical studies have shown a correlation between the degree of neoangiogenesis and the malignant potential of several cancers, including breast cancer and malignant melanoma. The aim of this study was to investigate a contrast-enhanced ultrasound method to evaluate the degree of neoangiogenesis in a rat sponge model. Since in this model, the sponge initially contains no blood vessels, any Doppler signals is indicative of neovascularisation.

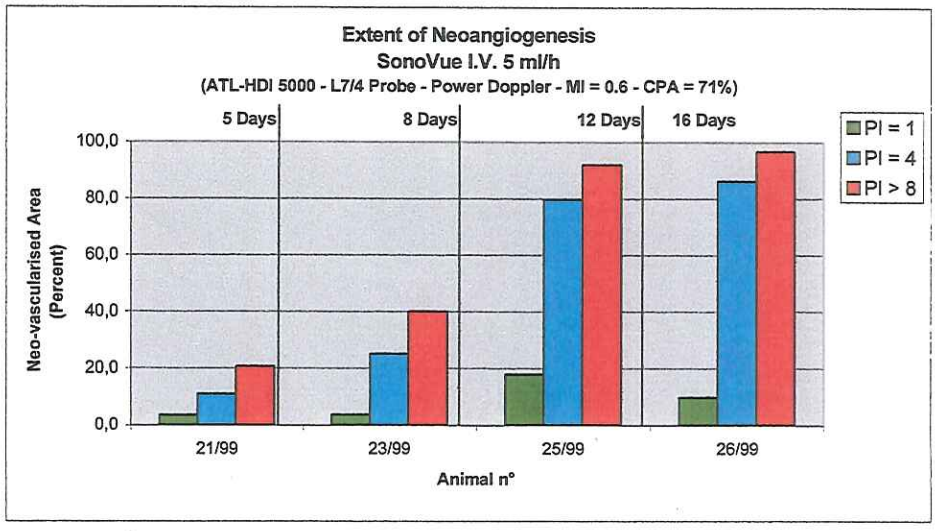
Male Sprague-Dawley rats received a subcutaneous dorsal implantation of sterile Mini-Swabs (Mod TX 761 Texwipe). Ultrasound examination was performed 4, 8, 12, 15/16, 20 and 23 days after the implantation using an ATL HDI 5000 scanner with a L7-4 linear array probe. The machine was operating in fundamental intermittent power Doppler mode at MI :0.6 and different pulsing intervals (1 s, 4 s, 8 s or 10 s) using an external trigger. During each examination, SonoVue™ was infused at a constant rate of 5 ml/h (Perfusor®fm Braun). Images were analyzed by means of a calibrated software tool (HDI-Lab ATL). The same region of interest (covering the whole cross sectional area of the implanted sponge) was used for all the acquired images whatever the day of observation following sponge implantation. Three quantitative parameters were used:

- Mean pixel level (in dB),
- Occurrence (pixel number/ level in dB),
- Neovascularised area (sum of pixels in Power Doppler/sum of pixels in GS).

SonoVue™ was shown to detect the appearance of neovascularisation within the sponge 8 days following implantation, in all the tested animals. Moreover, the use of an infusion of SonoVue™ and different pulsing intervals in intermittent Power Doppler mode allowed quantitative evaluation of neovascularisation in the sponge.


Neo-angiogenesis in rats bearing subcutaneous implanted swabs
(ATL-HDI 5000 - L7/4 Probe - Power Doppler - MI=0.6 - CPA=71%)
Day 8
PI = 1
PI = 4
PI = 10
32.1%
21.3%
6.2%
Pixels Number (Occurrence)
500.0
400.0
300.0
200.0
100.0
0.0
0
5
10
15
20
25
Video Intensity (dB)


Neo-angiogenesis in rats bearing subcutaneous implanted swabs
(ATL-HDI 5000 - L7/4 Probe - Power Doppler - MI=0.6 - CPA=71%)
Day 12
PI = 1
PI = 4
PI = 8
79.7%
91.8%
18.0%
Pixels Number (Occurrence)
500.0
400.0
300.0
200.0
100.0
0.0
0
5
10
15
20
25
Video Intensity (dB)


Extent of Neoangiogenesis
SonoVue I.V. 5 ml/h
(ATL-HDI 5000 - L7/4 Probe - Power Doppler - MI = 0.6 - CPA = 71%)
5 Days
8 Days
12 Days
16 Days
PI = 1
PI = 4
PI > 8
Neo-vascularised Area (Percent)
100,0
80,0
60,0
40,0
20,0
0,0
21/99
23/99
25/99
26/99
Animal n°

MYOCARDIAL PERFUSION IMAGING IN ACUTE MYOCARDIAL INFARCTION

Jaroslaw D. Kasprzak, Michał Plewka, Michał Ciesielczyk, Jaroslaw Drożdż

Dept. of Cardiology, Medical University of Łódź, Poland

Acute myocardial infarction is a clinical model of acute and complete thrombotic coronary artery occlusion. Emergency setting and the need to minimize a door-to-needle time preclude the use of nuclear perfusion imaging to verify a perfusion defect. On the contrary, myocardial perfusion echocardiography is a versatile bedside technique, which can be used without significant delay in the therapeutic management. However, data documenting safety and effectiveness of contrast echo are not available.

We present the initial experience with 4 patients (3 males, 1 female, mean age 53 years) imaged 3-24 hours from the onset of infarction pain studied on their initial presentation in our Department. After an informed consent had been obtained, the imaging was performed using Toshiba Powervision 7000 echocardiograph with 1.85/3.7 MHz harmonic probe in greyscale B-mode. Endsystolic triggered imaging at 1:3 - 1:5 intervals was used to visualize the perfusion defects. The contrast medium used was Optison, administered intravenously in boluses of 0.5ml up to the total dose of 3ml. The study was well tolerated and no adverse effects of contrast agent were observed. In all patients a well-defined defect was visible (in the territory of the right coronary artery - 1, left anterior descending - 2 and left circumflex - 1 patient), consistent with localization of infarction by ECG and definition of infarct-related artery by subsequent coronary arteriography. In 2 patients, a control study after revascularization proved the disappearance of perfusion defect.

In conclusion, initial experience with myocardial perfusion echocardiography is promising. The method appears to be safe and to introduce only a minimal delay in treatment. Confirmation of resting perfusion defect may be critical in patients with dubious ECG on presentation and can aid clinical decision-making leading to accelerated administration of fibrinolytics or percutaneous angioplasty. Verification of patency of the opened artery may also be feasible and practical with the new method.

CLINICAL EXPERIENCE WITH CONTINUOUS VS. BOLUS INFUSION OF INTRAVENOUS OPTISON™ DURING PERFUSION IMAGING (GATED VS. REAL-TIME)

Ostoic T., Puleo M., Gentil C., Sandelski J., Johnson M., Feinstein S.B.

Rush University, Chicago, IL, USA

Background: Myocardial perfusion imaging with contrast echo currently has been performed using gated imaging and bolus injections of intravenous contrast. In our institution we have performed myocardial contrast perfusion imaging on greater than 300 patients on two ultrasound systems (ATL HDI and GE/Vingmed) with correlation to angiographic data in 86 patients using bolus injections of intravenous Optison™ and gated imaging to every 4th cardiac cycle.

Hypothesis: Real-time imaging with power pulse inversion is now available on the ATL HDI 5000. Continuous infusion of Optison™ may allow better imaging of myocardial perfusion.

Methods: After consenting 10 patients undergoing routine transthoracic echocardiogram we imaged them using power pulse inversion. Our data and experience focused on dose and mode of infusion vs. parameters of machine settings (MI, focal zone, dynamic range and image orientation). 6ml of Optison™ was loaded into a Medix syringe injector pump. Continuous infusion of Optison™ was given at rates of 20, 30, or 40 ml/per hour. A continuous infusion of normal saline at 200ml/hour was intermittently infused.

Results: Visual assessment of myocardial perfusion using continuous infusion was demonstrated in all 10 patients.

Conclusion: Myocardial perfusion using continuous infusion of Optison™ and real-time imaging is a clinically useful tool. More work is needed to quantify myocardial perfusion using real time imaging.

A NEW TEST FOR PULMONARY ARTERIOVENOUS MALFORMATIONS?

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Departments of Radiology and *Thoracic Medicine, Hammersmith Hospital and Imperial College School of Medicine, London, UK

Aim: Changes in Doppler signal intensity can be used to quantify relative microbubble concentration. Doppler ultrasound is much more sensitive than grey-scale to the presence of microbubbles. We therefore hypothesised that quantitation of spectral Doppler signal intensity in the systemic circulation could be used to both detect and measure intrapulmonary shunting non-invasively.

Patients and Methods: To date, we have studied 18 patients with suspected PAVMs and 5 volunteers with full ethical approval. The patients all underwent quantitative radionuclide shunt studies with Tc99m microggregates, using a previously described technique, on the same attendance. Grey scale and spectral Doppler studies of the carotid artery were performed using an ATL HDI5000 scanner and an L12-5 probe. Two intravenous injections of agitated saline 10ml and one injection of Echovist 10ml 300mg/ml (Schering AG, Berlin) were made. (Echovist is a commercial microbubble agent, which does not survive transpulmonary passage to a significant extent.) The degree of enhancement – if any – was analysed subjectively on a 6-point scale. Where subjective enhancement was seen it was quantified by analysing the proportional change in Doppler signal intensity (units mV^2) on the audio output of the ultrasound machine. (Example: see below)

Results: One patient was excluded as the injection tissued. Of the remaining 17 patients, 11 had evidence of shunting (defined as shunt fraction>3.5%). All showed subjective enhancement with both agitated saline and Echovist. By contrast, no control showed enhancement. Of the 6 patients who were negative on the radionuclide study, 5 were negative on the ultrasound study. One such patient with a strong suspicion of a small shunt on pulse oximetry was positive with Echovist but negative on the isotope study suggesting that ultrasound may perhaps be more sensitive to small PAVMS. Analysis to date suggests an approximately linear relationship between shunt fraction and proportionate signal rise.

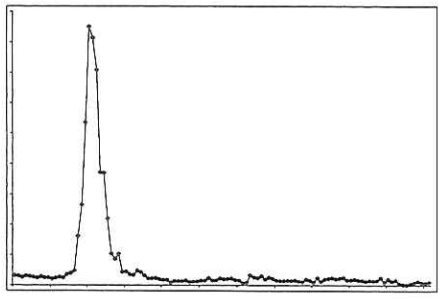

Figure: Doppler signal intensity versus time (units of 10s after injection of Echovist 10ml) There is a 28 fold rise in the signal intensity. Shunt fraction was 29%.

Summary: This relatively simple non-invasive test appears highly sensitive and specific. It may be possible to quantify shunt fraction with quantitative Doppler intensitometry; this could be of value in other imaging applications.

LOW MI PERFUSION IMAGING:
SOME CLINICAL EXAMPLES OF LIVER IMAGING

Peter Burns

Sunnybrook Health Science Center, Toronto, Canada

QUANTITATIVE POWER DOPPLER TECHNIQUE OF MYOCARDIAL CONTRAST ECHOCARDIOGRAPHY FOR DETECTION OF SEGMENTAL MYOCARDIAL PERFUSION DEFECT

Youssef F.M. Nosir, Tjebbe W. Galema, Ron T. van Domburg, Folkert J. Ten Cate
Heartcenter, Zuiderziekenhuis, Rotterdam, The Netherlands and
Cardiology Department, Al-Azhar University, Cairo, Egypt

Myocardial contrast echocardiography (MCE) with harmonic power Doppler (PD) technique has been recently introduced for qualitative assessment of left ventricular (LV) myocardial segments with normal and abnormal perfusion. The aim of the present study was to validate quantitative PD technique for accurate assessment of LV myocardial perfusion profile with MCE.

Method: Nine patients with LV myocardial infarction were recruited for this study. MCE studies were performed using ATL-HDI 5000 with intravenous infusion of Levovist (300 μg/ml) at a rate of 2 ml/m. Images were acquired from apical windows with harmonic PD mode at stepwise increase triggering intervals (1 to 9 beats) at end-systole. Images were scored for wall motion (WM) {16 segments model, (1 = normal, 2 = mild hypokinetic, 3 = severe hypokinetic, 4 = akinetic and 5 = dyskinetic)} as well as for subjective visual estimation (VS) of LV perfusion profile (1 = normal, 0.5 = partial and 0.0 = no perfusion). Images were digitized and stored for off-line quantitative PD analysis.

Results: A total of 216 segments were analyzed, the mean ±SD of MCE PD (db) quantitation were 31±8.4, 9.1±3.0 and 3.3±1.7 for LV cavity, LV myocardial segments with normal and abnormal perfusion, respectively. There was significant difference between quantitative PD of LV cavity and normal seg,ments (p=0.00001), and between normal and abnormal perfused segments (p=0.0001). When segments compared according to WM score, the mean ±SD of PD (db) were 7.6±3.6 and 3.3±2.2 (p=0.00001) for normal and abnormal segements, respectively. Abnormal segments were classified according to WM and VS scores and compared with PD measurements of normal segments (Table).

	PD according to WM					PD according to VS		
	1	2	3	4	5	1	0.5	0.0
Mean ± SD	7.6±3.6	3.8±2.4	2.3±0.9	3.2±2.2	-	9.1±3.0	4.3±1.9	2.4±0.9
p		0.0002	0.00001	0.01	-		0.005	0.00001

Conclusion: Quantitative PD analysis omits the the limitation of subjective visual analysis of MCE and provides accurate objective differentiation between normal and abnormal perfusion profile of LV myocardium.

Congres Location: Inntel Hotel
From Central station
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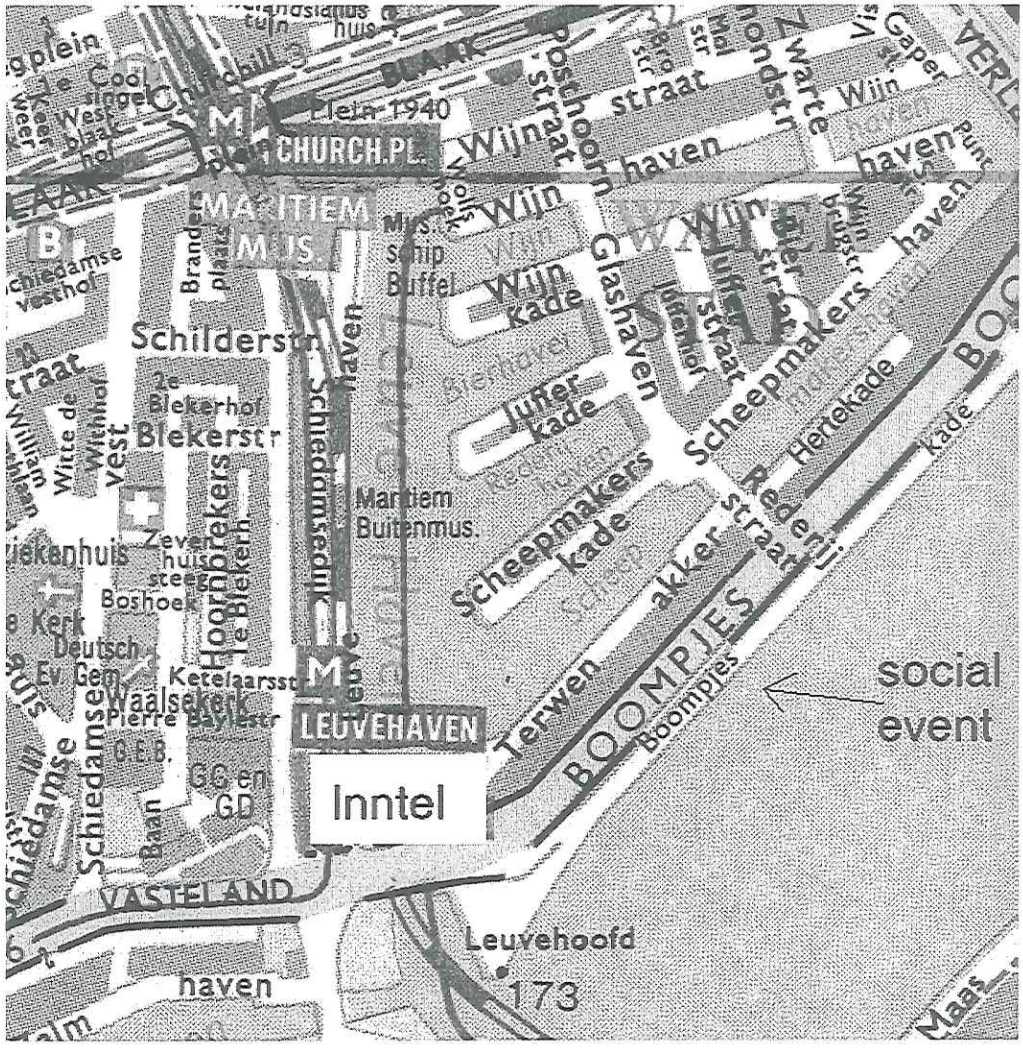
Bubbles on the River
Social event: Five minutes walk from the Hotel to ship "Thalassa Royal" for a Boat tour on the River Maas to the Harbor of Rotterdam, the largest port in the world (see map below).



5th HEART CENTRE EUROPEAN SYMPOSIUM ON ULTRASOUND CONTRAST IMAGING
19-21 JANUARY 2000, Rotterdam, The Netherlands.

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6th HEART CENTRE EUROPEAN SYMPOSIUM ON ULTRASOUND CONTRAST IMAGING
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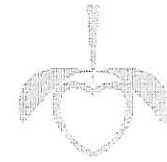

Rotterdam, January 2000

6 TH ULTRASOUND

CONTRAST SYMPOSIUM

24, 25 AND 26 JANUARY 2001

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