3rd Thoraxcenter European Symposium on Ultrasound Contrast Imaging

Abstractbook

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January 22 - 23, 1998 Rotterdam - The Netherlands

3rd THORAXCENTER EUROPEAN SYMPOSIUM ON ULTRASOUND CONTRAST IMAGING. 22 AND 23 JANUARY 1998, Rotterdam, The Netherlands.

WEDNESDAY	**21 January 1998**	
18.00 - 20.00	**Registration and Welcome drinks**	**Inntel Hotel**
THURSDAY	**22 January 1998**	
08.00 – 09.00	**Registration**	
Prof. N. Bom	Opening address	
09.05 – 10.30	**CARDIAC** ..... *Chairpersons: C. Breburda and S.Feinstein*	
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S. Iliceto	Myocardial microvascular integrity and the no-reflow phenomemom assessed by contrast echo.	5
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P. v.d. Wouw	Specific characteristics for imaging with Quantison	9
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10.45 – 12.15	**NON CARDIAC** ..... *Chairpersons: M. Monaghan and K. Ferrara*	
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FRIDAY **23 JANUARY 1998**

08.00 – 08.30 **Registration**

08.30 – 10.15 **INDUSTRIAL RESEARCH** ..... *Chairpersons: N. de Jong and F. Moriyasu*

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Y Mine — Harmonic flash echo imaging 54

J. Powers — Contrast quantification methods 55

E. Gardner — Tissue harmonic imaging 56

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and Intermission

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First announcement 1999

MYOCARDIAL PERFUSION AND FUNCTION USING CURRENT TECHNOLOGY ADVANCES

A. Distante and D. Rovai

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The introduction of contrast echocardiography into the clinical arena is bringing about a number of questions that are related not only to the new agents but also to the new ultrasonic techniques.
On one side, it is becoming evident that myocardial perfusion by contrast echocardiography benefits from new modalities to insonate, analyse and display the ultrasound signals (i. e. second harmonic, intermittent imaging, power mode, 3-D reconstruction, etc).
On the other side, the introduction of new technologies, such as harmonic imaging, can improve to such an extent the signal-to-noise ratio and the capability to detect endocardial interfaces that contrast agents may appear less needed or even pleonastic when cardiac function is the target of interest.

Myocardial Contrast Echocardiography: Myocardial perfusion at rest and during stress adds value to the assessment of patients with coronary artery disease where conventional echocardiography provides already information on regional function at rest, on effort and during pharmacological stress testing.
Despite the cost/effectiveness is to be proven and the costs are to be objectively quantified with ad hoc studies, it is foreseeable that the recent developments in ultrasound technology and contrast agents will permit physicians to assess myocardial perfusion by echo in patients with known or suspected coronary artery disease. The need is there and the fields where contrast agents for myocardial perfusion could impact the practice of modern cardiology are so relevant that a competitive race is on for the:

- assessment of acute myocardial infarction (diagnosis, measurement of risk area and infarct size, success of reperfusion, residual viability, collateral flow, etc);
- detection of coronary artery disease in stable outpatients (physiological significance of stenosis, assessment of myocardial viability in chronic disease, prognostic impact, etc);

- efficacy in the operating room (adequacy of cardioplegia, success of graft placement in conventional and key-hole surgery);
- quantification of myocardial perfusion (bubbles behaviour in microcirculation, myocardial blood flow and volume, bubble destruction and measurement of myocardial blood flow).

Endocardial border enhancement: The cost-effectiveness of contrast echocardiography in improving LV endocardial border definition will find his battle field in stress echocardiography. During pharmacological and exercise stress testing, a better capacity to determine presence or absence of abnormalities can increase specificity and can reduce: a) the number of *non-diagnostic* tests, and thus the need of redundant/confirmary imaging procedures (often more expensive, such as thallium scintigraphy); b) the number of unnecessary coronary arteriographies which may stem out also from poorly analysed stress echo testings, read as *positive* (abnormal motion) rather than uninterpretable.

The intravenous administration of a contrast agent may also improve the reproducilibilty of quantitative analysis of LV function: in fact, the estimation of the end-systolic volume at exercise is improved significantly and the estimated ejection fraction values are higher compared to values obtained from non-contrast investigations.

Improvement of endocardial border definition would also help to enhance the acceptance of echo data among the non echocardiography community: primary care physicians, internists, anesthesiologists or cardiovascular surgeons, etc may increase their confidence in the examination and in the opinion of the consulted echocardiographer.

The ideal target of a new imaging modality is not only to be aesthetically and visually more attractive but also to be *rich* in diagnostic content.

A number of technologies for improving endocardial edge definition and hence the accuracy and acceptance of stress echocardiograms have been implemented: high frequency transducers, color encoding, Doppler tissue imaging, color Doppler, harmonic imaging and contrast echocardiography. Several methodologies are machine specific and attempt to improve endocardial edge definition by post processing of ultrasound images. Others, such as tissue harmonic imaging, represent a new way to handle the ultrasound images. All these techniques are under intense investigation, in order to prove the efficacy in enhancing accuracy and confidence of interpretation.

In the case of stress echo, this would imply an improved ability to localize the LV endocardium and track the endocardium for development of abnormalities during the test. aesthetics of an ultrasound image but unfortunately creates diagnostic artifacts.

No doubt that of all the modalities potentially usable with stress echo, contrast echocardiography perhaps shows the greatest potentialities. The incoming (and growing) data on the role of contrast echocardiography in conjunction with cardiovascular stress have been concordant in suggesting an enhanced degree of accuracy.

A major question will be if harmonic LV imaging - even without contrast - is capable to enhance significantly the visualization of endocardial border. Another question will be if the use of contrast will improve the visualization of segments in a uniform manner or rather some (apical ones) better than others (basal ones) LV segments, due to attenuation.

An additional clue for future large scale use of contrast agents might come from the introduction of 3-D techniques: in fact, myocardial contrast enhancement significantly improves LV mass calculation with three-dimensional echocardiography and accurately delineates the perfusion defects regardless of their location. Furthermore, recent developments connected to new modalities of display and to potential uses of contrast agents - such as assessment of microvascular endothelial injury, visualisation of intramyocardial coronary arteries, site-specific microbubble adherence and drug/gene delivery, detection of intraventricular masses - added to the more traditional capacity to enhance Doppler signals and improve endocardial border delineation, might change the all picture to such an extent that what is considered sound now, could be completely overcome or overthrown by different and scientifically strong and solid evidence.

MYOCARDIAL PERFUSION USING FS069 (OPTISON™)

H. Dittrich

Mallinckrodt Medical GmbH, Germany

Albumin-based ultrasound contrast agents are a class of agents which differ from other agents in that they are fully manufactured initially and do not require any pre-activation by the clinician. Because of the Albumin microsphere shell, the possibility of "bubble" coalescence and therefore microcirculation obstruction is avoided. Albunex®, the air-filled microsphere has been followed by Optison™, a perfluropropane filled Albumin microsphere. In Phase 3 studies, Optison™ was shown to be superior to Albunex® for all cardiac function endpoints. In coronary artery disease patients undergoing pharmacologic stress studies harmonic imaging with off-line image post processing demonstrated concordance at approximately 86-90% while that for harmonic, non-processed images, the concordance rate was 71-86%. The use of Optison™ in exercise stress studies allowed 90% of unreadable non-contrast studies, at rest, to go on to stress (according to blinded read) where the agreement with nuclear studies was good for both unprocessed fundamental and harmonic imaging.

Further refinements in the manufacture and composition of albumin based agents has been undertaken raising the possibility of perfusion imaging in both fundamental and harmonic modes without the need for image processing. Experimental studies with new formulations have demonstrated the ability to follow dynamic changes in myocardial perfusion after clearance of the left ventricular cavity.

MYOCARDIAL MICROVASCULAR INTEGRITY AND THE NO-REFLOW PHENOMENON AS ASSESSED BY CONTRAST ECHO

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Both early reperfusion and adequate collateral circulation favours blood flow supply to the myocardium during prolonged myocardial ischemia although through different vessels (infarct-related artery, another coronary artery), thus limiting the development of irreversible myocardial damage. After myocardial infarction, restoring blood flow has been shown to be of beneficial functional effect also in patients in whom infarct-related artery is reopened by percutaneous coronary angioplasty some weeks after myocardial infarction. Recently the myocardial contrast echocardiography has demonstrated to have an important role in this context. In fact, in the acute phase, a microvasculature tracer like the myocardial contrast clearly delineates the risk area (as non opacified myocardium) and, after reperfusion, it indicates the extent of myocardium within the risk area in which microvasculature has not been destroyed by prolonged ischemia and that consequently has a potential to functionally recover if adequately reperfused (viable myocardium).

At the time of coronary reopening, intramyocardial reperfusion is achieved only in areas with anatomically preserved microvasculature, while reflow does not occur in myocardium with post-ischemic microvascular network damage. This failure to achieve uniform reperfusion after prolonged ischemia has been named "no reflow phenomenon". Myocardial contrast echocardiography being an indicator of microvascular integrity and myocardial perfusion, has been used before reperfusion for the assessment of the risk area; soon after reperfusion (15 minutes) myocardial contrast echocardiography is more sensitive than the angiographic demonstration of infart-related artery patency for the evaluation of the effective intramyocardial reflow. "No reflow" phenomenon is more common than previously thought, has a dynamic nature (its extent can increase or decrease in the first two weeks after acute myocardial infarction) and can be limited or even abolished if Verapamil is timely administered (at the time of reperfusion beginning). This beneficial effect on "no reflow" phenomenon is likely due to its antispastic effect on microcirculation.

Microvascular integrity, moreover, is an indicator of viability. In patients with acute anterior myocardial infarction, those with "no reflow" have a worse average segmental score and lower left ventricular ejection fraction than to those with " reflow", one month after acute myocardial infarction. Recent observations in our laboratory have also shown that myocardial contrast

echocardiography-enhanced post myocardial infarction dysfunctioning segments are more likely to improve their motion in response to dobutamine infusion.

Moreover, myocardial contrast echocardiography is accurate in mapping the extent of collateralized myocardium, the territory with double possible perfusion (either anterograde or coming from a different donor artery). So, if the native coronary artery is occluded, the injection of sonicated contrast medium in the other artery can show myocardial opacification in segments within the occluded artery perfusion bed. If the native coronary artery is reopened, the real extent of its perfusion bed can then be estimated with infarct related artery contrast injection (myocardial contrast echocardiography opacified area). The myocardium that is opacified by injections both in infarct related artery and in the other coronary arteries represent the collateralized one.

Myocardial contrast echocardiography has the potential to identify such a condition since it allows evaluation of microvasculature flow conditions after infarct related artery reopening and therefore the identification of "no reflow" phenomenon, comprehension of coronary anatomy and myocardial perfusion relationships and, consequently, identification of the coronary artery supplying blood flow to the dysfunctioning myocardium and immediate identification of "reflow" effect of coronary angioplasty of an occluded infarct related artery by observing echocontrast opacification of myocardium after its injection in the reopened infarct related artery.

VALUE OF CONTRAST FOR THE CLINICAL ASSESSMENT OF ISCHAEMIA DURING STRESS ECHOCARDIOGRAPHY

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Stress echocardiography has become a popular modality for the assessment of patients with known or suspected coronary artery disease. In addition to contributing to the diagnosis of coronary artery disease, its great contribution is the assessment of functional significance of a coronary stenosis in terms of presence and extent of ischaemia as well as the presence of recoverable myocardium when resting ventricular dysfunction is present. In order to obtain however the most reliable diagnostic information from a stress echocardiography, it is important to clearly visualise the entire endocardium which often may be difficult. The use of transpulmonary contrast agents has revolutionised modern echocardiography, particularly with the enormous potential of providing information on myocardial perfusion. A number of agents have proven their ability to distribute in the myocardium following the myocardial blood flow distribution. This provides us with the potential to utilise transpulmonary contrast enhancers during routine stress echocardiography in order to improve endocardial border detection and identify underperfused areas.

There is no doubt the vast majority of transpulmonary agents are able to improve endocardial border delineation and we have tested this hypothesis with agents such as InfosonTM, Sonovue TM, Echogen" and NC100100 (Nycomed Imaging, Norway). However, a number of recent studies have also demonstrated that the simple utilisation of 2nd harmonic imaging with state-of-the-art ultrasound equipment is also in the position to improve endocardial border detection during stress echocardiography without the need for adding a contrast agent. It is therefore essential to demonstrate additional myocardial opacification during stress and even better myocardial perfusion deficits during stress. We have todate demonstrated the presence of resting myocardial perfusion abnormalities in patients with previous myocardial infarction in 22 patients undergoing myocardial contrast echocardiography (MCE) with NC100100. Amongst 203 normally contracting myocardial regions, 151 (74%) were normally perfused by 99mTc-MIBI SPECT and 145 (71%) by MCE. With SPECT, abnormal tracer uptake was mainly found among normally contracting segments from the inferior wall. Conversely, with MCE poor myocardial opacification was noted essentially among the

normally contracting regions from the anterior and lateral walls. Of the 142 dysfunctioning regions, 87 (61%) showed perfusion deficits by SPECT and 94 (66%) by MCE.

Excluding attenuation artifacts improved both sensitivity (76%) and specificity (83%) of the detection of SPECT perfusion defects by MCE.

It would appear that dipyridamole stress provides a better myocardial contrast enhancement than exercise or dobutamine stress echocardiography as opposed to better myocardial contraction abnormalities during exercise or dobutamine. It seems that dobutamine echocardiography will provide the best compromise in order to obtain the most benefits from both,myocardial opacification and contraction during stress.

INFUSION VERSUS BOLUS INJECTION OF QUANTISON™ FOR MYOCARDIAL OPACIFICATION

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Myocardial contrast echocardiography requires an imaging approach that differs from blood pool contrast imaging , due to the relative low volume of blood in the myocardium. One of the variables is the concentration of contrast. During bolus administration the contrast concentration changes continuously from absent to an early peak and gradually diminishing.

Especially when this happens over a short period of time (0.5 to 1 minute) it can be difficult to obtain the required images and impossible to do quantitative studies. With continuous infusion of a contrast agent itshould be possible to obtain a steady state that allows for an extended imaging period and quantitative imaging. We therefore conducted a dose-finding trial with continuous infusion of Quantison™ in 10 volunteers, and a further trial comparing bolus versus infusion in 9 volunteers. All volunteers were healthy males aged 19 to 35. In the dose-finding trial each individual received three infusions using three of the following doses: 0.2, 0.5, and 1.0 or 1.5 ml/min. In the bolus versus infusion trial a bolus of 1.0 ml was used, and an infusion of 1.0 ml/min. Infusion continued for 20 minutes. An ATL HDI 3000 with second harmonic imaging and an MI of 1.5 was used in EKG- triggered mode to obtain contrast images. Myocardial opacification was assessed visually and by videodensitometry of digitized S-VHS tape recordings of 4-chamber views in a 6-segment model. Myocardial opacification was present in all volunteers. During continuous infusion intramyocardial contrast started to appear after 1-2 minutes of infusion and images were optimal after 3-4 minutes. With the higher dose levels attenuation due to contrast in the left ventricle started to occur after 10-12 minutes of infusion. A dose of 1.0 ml/min was the optimal concentration in these volunteers, and was used in the design of the bolus versus infusion trial. Although infusion offered the advantage of an extended imaging period and possibly of quantitating contrast data, it was possible to obtain adequate images with bolus injections in all nine volunteers.

ULTRASOUND CONTRAST ASSESSMENT OF LIVER DISEASES

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Introduction: There are two ideas which are expected to be useful in assessing liver diseases using ultrasound contrast enhancement. One is morphological and the other is functional assessment. The morphological assessment means detection of vascular and parenchymal abnormalities by enhancement. The functional assessment includes quantitative analysis of blood perfusion of the tissue and also functional assessment of phagocytosis of microballoon particles by Kupffer cells.

There are differences in characteristics of microbubbles used for diagnosis of liver diseases. Vascular and parenchymal enhancement have an important role in diagnosis of liver diseases especially localized space occupying lesions in the liver. This is dependent not only on differences of perfused blood flow rate of each tissue but also on blood supply of the tissue, hepatic arterial and portal blood flow.

In this paper, the assessment of neoplastic diseases of the liver using contrast enhancement will be discussed especially focusing on malignant neoplastic diseases of the liver.

Contrast Agents Suitable for Liver Imaging

There are still unknown issues about behavior of microbubbles in the liver. Not only small sized resistive (strong) microbubbles such as SonovistTM but also vascular enhancers which size is too large to be phagocytosed by Kupfer cells but too small to be embolized in the capillary beds are observed to be trapped in the liver. The stagnancy of the microbubbles in the liver can be explained by phagocytosis in some cases and by stickiness to the sinusoidal endothelium in other cases. OptisonTM is trapped and erased out from the hepatic parenchyma and observed very little in the hepatic veins even without exposure of ultrasound. However, its does not accumulate in the liver. On the other hand, NC100100 and OUC82755 which is composed of lactic acid polymer shell and perfluorocarbon gas are accumulated in the sinusoidal space (?) for long time if the ultrasound is not emitted.

Many of the microbubbles are easily destroyed by ultrasound exposure even at the diagnostic level as MI value is less than 1.9. This fact means the same thing that the microbubble is easily visualized by harmonic imaging system when the microbubble is fragile to ultrasound exposure. In other words, it is difficult to see microbubbles if they is too strong to be destroyed though they can survive longer in circulating blood. There is the dilemma and it should be resolved by development from three sites; development of pharmaceutical, instrumental and scanning techniques.

Harmonic Gray Scale Enhancement in Diagnosis of Liver Tumors

Enhancement of gray scale imaging with contrast agents is a fascinating method because it has a high spatial and temporal resolution and the signals are not dependent on velocity of the microbubbles flowing in blood. When the agent is injected intravenously, hepatic arterial blood flow is enhanced 15.0 + 3.4 seconds after injection and portal blood flow is enhanced 21.6 + 7.3 in human patients. Therefore tumor vessels are enhanced in the early arterial phase because main feeder of the tumor blood flow is from hepatic artery. The differentiation between malignant and benign tumors is easy in most cases by observing early opacification of the parenchyma of the tumors, in which blood perfusion rate is faster than benign tumors even though blood flow of the benign tumor is supplied by hepatic artery such as in hemangioma.

Transient Scattering Imaging (Flash Echo Imaging) of the Liver.

Suspension of scanning for a certain period makes us to obtain more signals from the tissue than by continuous high frame rate scanning. This is used for enhancement of both color Doppler and harmonic gray scale imaging. It takes several seconds to re-fill the hepatic parenchyma with fresh blood carrying new microbubbles which were not exposed by ultrasound in a certain slice. The amount of signals in transient scattering mode is dependent on three factors. The first is concentration of microbubbles in the flowing blood. The second is perfusion rate of the tissue (% of re-perfused volume / second). The third one is vascular space of the tissue (vascular space / tissue volume).

These factors vary from case to case examined. Specific features seen in the malignant tumors of the liver are hypervascularity and high perfusion rate comparing with non-tumor parenchyma. In the case of hypervascularity in hepatocellular carcinoma does not mean always high perfusion blood flow (ml/g tissue/min). When we call hypervascularity in HCC, it means $B%a_(Jarterial

hypervascularity_$B%b_(J. Total blood flow from the hepatic artery and the portal vein is not increased in HCC because the normal sinusoids are supplied by rich portal blood flow, about 1 ml/g/min. It is possible to enhance only the malignant tissue by modifying these factors and suppress the non-tumor tissue enhancement.

Conclusion: Intravenous enhancement with microbubbles is an useful diagnostic modality for liver diseases, especially malignant liver tumors and it will replace dynamic CT in almost all cases of liver tumors because of its high sensitivity and specificity.

HARMONIC CONTRAST ECHO FOR ISCHEMIC NEUROLOGICAL DISEASE

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Potentials of harmonic imaging were evaluated in two studies involving 12 human volunteers using a HP Duplex system (Sonos 2500) connected with a 2.5MHz (for conventional imaging) and a 1.8/3.6 MHz (harmonic imaging) sector transducer. Grey scale images were established in the transient-response mode.

In the first part ultrasound densities in the thalamus (THAL), the temporo-parietal white matter (TPWM) and the lateral fissure (LF), where branches of the middle cerebral artery are located were quantified by means of acoustic densitometry. Time density curves were calculated after application of 10ml BY963 for a period of 60 x 5 heart cycles. Based on this curve, increase of intensity (dB) as well as the area under curve (AUC; dB x 5hc) were calculated.

Results: Mean increase (± SD) and mean AUC (± SD) from baseline in the region of LF, THAL and TPWM were 2.2 ± 1.7, 1.1 ± 0.6 and 0.9 ± 0.9 dB as well as 16.7 ± 22.7, 4.7 ± 4.7 and 3.7 ±6.3 dB x 5hc, respectively. There was a statistic difference for mean AUC ($p=0.02$, $n=12$) in the three regions of the brain but not for the mean intensity increase ($p=0.07$).

In *conclusion* this study indicates that different regions of the human brain show different time-density curves with significant differences of AUC using harmonic imaging. This is consistent with the known regional differences of physiological perfusion in these cerebral regions and indicates that it is possible to measure relative perfusion differences in various regions of one arterial territory in the adult human brain.

In a second clinical part we compared harmonic imaging with conventional color Duplex imaging in the vertebrobasilar circulation. 6.5 ml Levovist ™ (400 mg/ml) was used as a contrast agent.

Results: Harmonic imaging allowed to detect more cerebellar arteries (35 vs. 31), the duration of blooming artefact was significantly reduced (7.9 vs. 29.9 seconds, $p=.03$), the duration of diagnostic useful signal enhancement was increased (248.5 vs. 117.4 seconds, $p=.0003$), but the maximal investigation depth was reduced (8.4 vs. 9.3 cm, $p=.001$). There was a significant difference in the

systolic blood flow velocity in the vertebral and basilar artery comparing conventional and second harmonic Duplex ($p<.04$).

In *conclusion* second harmonic color Duplex imaging in the vertebro-basilar system increases the time of diagnostic useful signal enhancement and produces a better spatial resolution compared with conventional color Duplex imaging.

EXPLOITATION OF NON LINEAR RESPONSES IN RADIOLOGY

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Current radiological uses of microbubbles rely on the increase in signal intensity that they produce, usually in the Doppler mode because of its better sensitivity. While non linear modes can also be used in the same way, by detecting a microbubble signature, they offer the possibility of demonstrating microbubbles that are very slow moving or even stationery, so that blood in tissue capillaries could, in principle, be detected. Two such phenomena have been discovered and radiological exploration of their uses is just beginning. These are the harmonic and the scintillation (stimulation acoustic emission) responses, phenomena that are related by their dependence on the need to deposit a sufficient amount of acoustic energy to excite the microbubbles to extreme oscillations. Full exploitation will depend on further collaboration between the manufacturers of the microbubbles and of scanning equipment, for these phenomena depend on an appropriate interaction between the sound beam and the microbubbles.

In the harmonic mode, the non linear excursions of the microbubbles causes them to produce overtones (harmonics), the second (x2 frequency) being the strongest. It is fortunate that modern transducers have sufficient band width to allow transmission at, say, 2MHz and receipt at 4MHz. In B-mode, harmonics increases the signal-to-noise ration, highlighting vessels and well perfused tissue against the background. In Doppler, blood flow is better seen because flash artifacts produced by tissue movement is suppressed. In both, there may be penalties of penetration and spatial resolution. An incidental consequence of harmonic microbubble imaging is the finding that tissue itself can give a harmonic response by virtue of the non linear propagation of ultrasound. Because ultrasound travels faster through the denser tissue during the compression phase of the ultrasound travelling wave, the compression phase tends to overtake the rarefaction phase and the original sign waves become distorted, thereby acquiring overtones. This effect takes a few centimeters of travel to develop and so a system set to operate in harmonic mode (without microbubbles) shows weak signals near the skin and therefore reverberation artifacts are minimized. Because the non linear propagation depends on the pressure amplitude generated, it is less marked at lower ultrasound power. This has the useful effect that the weak side lobes produce less harmonic intensity than the main beam so that

the beam profile is improved. Overall, the reduction of reverberation and side / grating lobe artifacts cleans up the B-mode picture, especially for "difficult" subjects.

If the transmit power is increased further, microbubbles (especially the relatively unprotected types) undergo extreme expansion and contraction and this may so alter their structure that they stop resonating (perhaps because their membrane is different or because they fracture). The disappearance of a microbubble from a beam between sequential Doppler pulses is interpreted by the scanner as a sudden movement which is depicted on colour Doppler as an extreme colour change. In real time, this gives a scintillating appearance to the colour Doppler velocity scan with a mosaic of different colours from adjacent pixels (sometimes termed stimulated acoustic emission). This occurs just as well with stationery as with moving microbubbles. The most dramatic scintillating agent is Sonovist, an experimental microbubble, but Levovist also produces the effect, albeit much more transiently. In both cases, there is an early vascular phase throughout the body followed by a late parenchymal phase restricted to normal liver and splenetic tissue. In this phase, lesions that were undetected before microbubbles administration become obvious. While the full evaluation of the clinical value of this method awaits further study, it seems to be promising as a way to detect isoechoic metastases. When stimulated in this way, the microbubbles are inactivated and this probably also occurs at lower ultrasound power. Bubbles destruction extinguishes the signal until the microbubble population in the ultrasound beam is refreshed by inflow of new microbubbles. In large vessels this happens sufficiently rapidly that the signal loss is usually insignificant but in tissue with its slow perfusion rate, the signals fade markedly depending on the microbubble structure and the acoustic power which is highest for Doppler and in the harmonic mode. If the pulse repetition frequency is lengthened to allow more complete regression, the signal from the next pulse is much more intense. In this "intermittent mode" (also known as "flash echo") grayscale enhancement can be seen with microbubbles agents that otherwise need Doppler for their detection. Intermittent imaging can be used in B-mode and in Doppler and can usefully be combined with harmonic imaging to increase the signal-to-noise ration further.

HAS CONTRAST ECHO ANY ADDITIONAL VALUE IN THE ERA OF NOWADAYS TECHNOLOGY

J.S.Lameris

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This presentation will focus on the role of ultrasound contrast agents for diagnostic studies of abdominal parenchymal organs. Since the availability of new US contrast agents consisting of small size microbubbles capable of surviving transpulmonary passage there has been a great interest of its potential role in US examination of abdominal organs. Especially the liver, the kidneys, their vascularisation and the splanchic (venous) vessels seem likely area's in which conventional ultrasound could benefit from the echo enhancing effect of contrast agents. The increased sensitivity to detect and characterize flow in normal and abnormal (tumor) vessels is generally seen as a new possibility to distinguish normal and abnormal tissue.

The question arises why these new contrast agents are so far from a wide clinical acceptance. The reluctance to abandon the non invasive character of ultrasound, the costs are, among others, answers to this question. The recent developments in ultrasound contrast agents coincided with important improvements in US imaging itself, like dramatically improved flow detection, which limits the indications for ultrasound contrast agents. Imaging modalities, like helical CT scanning and MRI underwent a similar development. These techniques rely heavily on the use of contrast agents, that evolve more and more to tissue specific agents. Fast data acquisition, nowadays, allows detailed study of contrast behavior in time.

Intrinsic differences between ultrasound imaging and other imaging modalities, therefore, seem to play an important role in the acceptance of ultrasound contrast agents. To study contrast behavior in tissue a fast, standardized, reproducible and reliable imaging method is required. Helical CT scanning and MRI seem to meet these requirements better than US. The short effective life cycle of ultrasound contrast agents, once injected, is seen as an disadvantage. The same problem, however, holds for many contrast agents for CT and MRI but has been accepted because of the unique qualities of these imaging modalities. Most of the diagnostic studies with ultrasound contrast agents done so far lack a reproducible design, standardized equipment, comparison with other imaging

modalities and hard clinical endpoints. Unless scientifically solid studies are undertaken and the added value of the use of us contrast agents is proven, it is hard to imagine that these new agents will change the diagnostic approach for abdominal organ disease.

ENHANCED DESTRUCTION OF MRX115 DURING IMAGING

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Enhanced detection of contrast echo myocardial signals by Power Doppler (PD) has been reported even though the velocities in myocardial capillaries (0.1-2 cm/s) are below the threshold for Doppler motion detection. Ultrasonic interrogation itself produces oscillations which may lead to bubble destruction. Nonlinear transient scattering during these events might generate a pseudo-Doppler shift even in the absence of bubble motion. We used PD on an ATL HDI 3000 imaging system to image the behavior of MRX115 (ImaRx Pharm) and QW7437 (Sonus Pharm) in a tube perfusion model. Four acoustic power outputs were studied (mechanical index [MI] 0.3, 0.5, 0.7 & 0.9) with isonation at 3 MHZ. Power Doppler imaging was performed in both harmonic (HRM) and nonharmonic (NHRM) modes while 0.5ml boluses of contrast were introduced into the model and flow halted during the imaging period. In all sequences, a Power Doppler with unique sparkling "microexplosions" was detected even in the absence of contrast movement. For the ImaRx agent the initial PD signal intensity and maximum decay rates were greatest at the highest MI in NHRM mode (Table). The pre-activated QW7437 agent behaved similarly but continued to generate new bubbles and PD signals as it vaporized. Bubble destruction associated with acoustic-stimulated power scattering may generate the Power Doppler signals detected in the myocardium.

	NHRM 0.9	HRM 0.9	**NHRM 0.7**	HRM 0.7	NHRM 0.5	HRM 0.5	NHRM 0.3	HRM 0.3
Max Intensity (vdu)	1.28	0.57	1.12	0.53	0.72	0.46	0.61	0.43
Max decay Rate (vdu/s)	12.84	3.4	6.5	2.13	4.06	0.21	2.63	0.29

HARMONIC IMAGING

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The development of harmonic imaging in diagnostic 2D ultrasound equipment started in the early nineties. It was initiated and primarily meant for better imaging of ultrasound contrast agents. Contrast agents consist of gas-filled microbubbles which are known for their non-linear vibration as function of the applied acoustic pressure. The development of harmonic imaging was expected to improve visualization of the agent.

It turned out that harmonic imaging was a modality on his own. The propagation of the finite-amplitude ultrasound wave through the human body creates non-linear components which can be detected with harmonic imaging. Harmonic images turned out to be very different from normal fundamental images and it is recognized that in many cases harmonic images are better than fundamental ones. The mean reasons are a smaller beamwidth, lower sidelobes, lower grating lobes (M. Averkiou et. al. 95 - Ward et. al. 97) and much less reverberations between the phased array transducer and skin/ribs of the human body. This results in a better definition in the near field and improved signal to clutter ratio. Non-linear propagation was already recognized a long time ago (Naugol'nykh et. al 1959). Hart and Hamilton in 1988, Bacon and Baker in 1989 and Ward et. al. in 1997 suggested that imaging of the non-linear component would improve the image quality.

The quality of images of ultrasound contrast agents made in the fundamental mode is clearly inferior to images made in the harmonic mode. It has been thought that this is due to the superior non-linear scattering properties of the contrast agents. However, harmonic images contain a summation of two scattering components. The first component originates from the non-linear propagation of the fundamental wave through tissue. The second one is due to the linear scattering of the non-linear component of the propagated ultrasound wave. Discrimination between these two components is important for complete understanding of the phenomenon.

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LEFT VENTRICULAR PRESSURE ASSESSMENT

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Ultrasonic contrast agents possess the potential to serve important measurement functions other than its current usage. Ultrasonic contrast agents consist of a plethora of microbubbles smaller than red blood cells and circulate in the blood pool altering the acoustic impedance of ultrasonic sound waves. Besides the now popular 2nd harmonic effects generated by these bubbles, bubbles have the potential to measure pressure noninvasively.

Bubbles and thin-walled capsules containing gas exhibit a dynamic response which means can be made to go into resonance. At resonance, the bubble's scattering cross-section increases markedly, thereby providing an opportunity to interrogate it. This resonant response is a function of pressure. Therefore, it is theoretically possible to measure left ventricular pressure from the bubble's resonant response.

The following items will be addressed during the talk:

How bubbles provide a measurement of pressure?
What are the required bubble properties?
Experimental results.

ACOUSTIC CHARACTERISATION OF CONTRAST AGENTS FOR MEDICAL ULTRASOUND IMAGING

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Nycomed's ultrasound contrast agent *NC100100* has been investigated by *in vitro* acoustic measurements. Acoustic attenuation spectra were used to determine resonance frequencies of the particles. The spectra were correlated with size-distributions, and it was found that the shell-encapsulated gas-bubbles can be described as visco-elastic particles with bulk modulus 700 kPa. When exposed to hydrostatic over-pressures mimicking those found *in vivo* during the systolic heart cycle, the resonance frequency increased, as expected by the particles' increased stiffness. This effect was reversible: After the pressure was released, the particles went back to giving the original attenuation spectrum. This shows that the particles are not destroyed or otherwise changed by the pressure. Acoustic backscatter measured as function of distance through contrast agent was used to estimate the backscatter efficiency of the particles, that is, the ratio between scattered and absorbed ultrasound. Results from these measurements agree with theoretical estimates based on the attenuation spectra. Measurements on *NC100100* were compared with earlier results from measurements on *Albunex* and measurements on an experimental polymer-encapsulated contrast agent, showing how different shell materials cause differences in particle stability and stiffness.

IN-VITRO AND IN-VIVO EVALUATION OF CONTRAST AGENTS DURING INSONATION

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A system has been developed which allows optical observation of contrast agents in a phantom or within the microcirculation during insonation. Microspheres can be repeatedly insonified and changes in the shell characteristics, gas content and location within a flow stream then documented. In this paper, we examine two phenomena associated with gas-filled microspheres, which are the escape of gas from the sphere during repeated insonation and the deflection of microspheres due to primary radiation force. The persistence of air-filled and perfluoropropane-filled microsphere has been measured and will be compared as a function of imaging parameters. We observe that the gas can slowly disolve into the surrounding solution during low-intensity insonation, or more rapidly exit from a defect in the shell during high-intensity insonation. In addition, the influence of radiation force on the motion of microspheres in a flowing stream will be detailed. Under both in-vitro and in-vivo conditions, a low-intensity high-prf acoustic pulse train can effectively manipulate contrast agents. The deflection of microspheres is documented for microvasculature with a diameter between 25 and 100 microns, demonstrating that in each case microbubbles can be deflected to the vessel wall with an acoustic pressure below 2 MPa.

CURRENT UNDERSTANDING AND USE OF STIMULATED ACOUSTIC EMISSION

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The term 'acoustically stimulated Acoustic Emission' was coined in 1994 to describe a special kind of transient ultrasound signal which can be used to detect contrast agents like SHU 563 A in a very sensitive way [1, 2]. Since then, the mechanism has been investigated in greater detail and was found to be applicable also to other contrast agents.

The effect, which is most pronounced at extremely low bubble concentrations, is transient on a time scale given by frame rates as used in cardiological imaging (typically 30 Hz). It implies that air microbubbles may disappear within less than about 30 milliseconds even if they were hit by only a single pulse of sufficient amplitude. These bubbles then can't contribute to the signal enhancement in the next video frames. However, several groups found by independent methods, that during the first 1-10 milliseconds the same microbubbles still would strongly respond to several other transmit pulses, as they are used in Color Doppler. This explaines why CD enhancement is best observed in the first frame of a sequence. It also indicates that air bubbles typically disappear by dissolution of gas. Fission of air microbubbles and formation of many smaller 'nano'bubbles should lead to even shorter lifetimes and to RF signals different from those which are actually observed in our experiments.

Once bubbles are destroyed, enhancement is reduced in all modes until new bubbles enter the ultrasound beam. In a vessel with 25 cm/s flow velocity transvers to the scan plane it requires about 4 milliseconds if the beam diameter is 1 mm. In this case signal enhancement would not be markedly affected. However, in smaller vessels with less than about 5 cm/s flow velocity the inflow of new bubbles would be slower than their destruction, resulting in a severe loss of enhancement in all modes. Moreover, in this case of slow 'reperfusion' the microbubbles have only time to enter the outermost part of the sound beam. This has two additional drawbacks: bubble shells may still be broken, but bubbles are only weakly excited at the rim of the sound field, and their response is received with lower sensitivity. Thus, average enhancement would be low in all following frames or pulses if the repetition rate is too high. Recently, detection sensitivity in harmonic modes could be

further improved by special pulse sequences that make use of the nonlinear response of scatterers. One method even claims to be non-destructive, but this remains to be confirmed.

Optimal detection of contrast agent requires adjustment of the (pulse or frame) repetition rate to the reperfusion rate in the region of interest. Preliminary results with Levovist® and other agents are quite promising. Tissue perfusion can be detected at least in a qualitative manner, if image acquisition rates (in a fixed scan plane) are less than about one image per second, e.g. in a ECG-triggered mode. This should not pose real problems in future 3D-modes where the scan plane is changing during image acquisition. In this case, scan plane movement can substitute flow of microbubbles. Results with current 3D technology are also encouraging.

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IDENTIFICATION AND LOCALIZATION OF STATIONARY GALACTOSE-BASED MICROBUBBLES IN VITRO USING TRANSIENT DOPPLER SIGNALS

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In many applications of medical diagnostic ultrasound the lack of intrinsic tissue contrast remains a problem. For Doppler detection of blood flow microbubble echo enhancing agents, working in fundamental resonance scattering mode, have helped with this problem but it would be very useful to have an echo signature that localized the contrast material in the absence of a Doppler shift due to blood flow.

Microbubbles designed to survive cellular uptake by virtue of a relatively thick protective polymeric shell (Sonovist™, SHU 563A, Schering AG) exhibit a strong, random signal on color Doppler images, even when stationary (Uhlendorf and Scholle, p.233 in Acoustical Imaging, Vol. 22, Plenum Press, 1996). This phenomenon, termed 'stimulated acoustic emission' by the authors, was believed to be associated with the cracking of the shell of the microparticles.

In this paper we describe a preliminary investigation that demonstrated, using a phantom in vitro, that random color Doppler signals can be made to depict the distribution of stationary Levovist™, a surfactant stabilized bubble. Microbubble suspensions were rendered stationary by injecting them into a viscous medium supported within a tube of latex rubber. These were then scanned with a SONOS 1500™ color Doppler scanner. The spatial distribution of microbubbles was visible on the B-mode sonogram and stable at low output power (20dB, arbitrary reference). The brightness of the echoes from the bubbles faded at higher power (25dB) and was not detectable after 3 to 5 min.

Bubbles ceased to be visible within 0.5 sec when the system was switched to color Doppler mode, during which time they appeared to emit a flash of color Doppler signal. This color Doppler signal was localized to the region of bubbles seen in B-mode. Background scattering particles, deliberately included in the phantom, confirmed that no large scale unidirectional bulk motion had occurred.

Although irreversible, the whole sequence of events was easily repeatable by scanning a new region of the phantom. Computer analysis of the time course of various quantitative features of the Doppler images was carried out but as yet has not revealed specific evidence for a preferred mechanism for the phenomenon. This is something that we are continuing to study.

PREDICTING ACOUSTIC RESPONSE OF A MICROBUBBLE POPULATION FOR CONTRAST IMAGING

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Introduction: Understanding non-linear scattering of moderately strong (100 kPa) ultrasound by contrast agent microbubbles is key to the success of harmonic imaging and other non-linear imaging techniques. Most of the research to date has been focussed on empirical measurements of various parameters of contrast agents *in vitro* and *in vivo*. Although most mechanisms governing the behaviour of a bubble in an acoustic field are well understood, a gap exists between theoretical understanding and actual application to clinical contrast imaging. Notably, very few theoretical studies to date attempted to simulate response from bubbles with a realistic size distribution. In this paper, we present a theory for predicting acoustic response of a bubble population for contrast imaging by combining numerically simulated echoes from an ensemble of bubbles with a realistic size distribution in a sound beam of realistic geometry.

Theory: There are three key components to the present model. First, the dynamics of the radial motion of a bubble was simulated by numerically integrating an equation similar to one by Trilling:

$$R\left(1-2\frac{U}{c}\right)\dot{U}+\frac{3}{2}\left(1-\frac{4U}{3c}\right)U^2-$$
$$\frac{R}{\rho c}\left(1-\frac{U}{c}+\frac{U^2}{c^2}\right)\dot{P}=c^2\ln\left(\frac{P+\rho c^2}{p_\infty+\rho c^2}\right)-\frac{R}{\rho c}\dot{p}_\infty,$$

where R is the radius of the bubble and $U=\dot{R}$; P is the pressure of the liquid at R; ρ and c are the density and speed of sound of the liquid; and $p_\infty(t)$ is the incident pressure. Trilling's model, like the Rayleigh-Plesset model, is based on consideration of the fundamental processes governing bubble motion. The key difference is the assumption that the liquid phase is slightly compressible so that acoustic wave propagation is linear. The Rayleigh-Plesset model assumes that the liquid is incompressible. It has been demonstrated that Trilling's is significantly more accurate than the Rayleigh-Plesset model even with an acoustic damping term. As bubble response (such as resonant frequency and scattering cross-section) to short pulse incident wave deviates significantly from

continuous wave response, the incident waveforms used in our model were recorded from hydrophone measurements from a real focused disc transducer.

Second, individual bubbles are well-known to have a narrow resonant frequency peak, while experiments demonstrate that most contrast agents have a very wide frequency response. This is due to the range of bubble sizes that exists in an agent, therefore, simulation at any single bubble size cannot be accurate. Our model contains a random ensemble of bubbles with a size distribution of that of an actual agent (figure 1a).

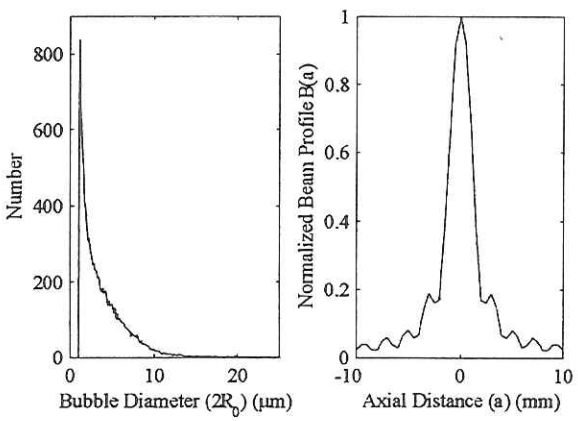

Figure 1: *Measured bubble size distribution and measured lateral beam shape used in the model*

Finally, an ultrasound beam interferes with itself and with the bubbles to form speckle in images. This process is in principle the same one that produces tissue speckle. However, as the bubble response depends nonlinearly on incident amplitude, the speckle formation process becomes nonlinear also. In particular, the amount of harmonic emission may be influenced by the beam shape. In our model, each bubble is given a radial position a and an axial position z. The incident pressure waveform for each bubble is scaled according to its radial position and the beam shape (figure 1b). The radiated pressure waveforms calculated for each bubble are again scaled by the beam shape and time-shifted according to its axial position and summed to give a ensemble echo, as illustrated in figure 2. The sample volume is short compared to the focal depth of typical transducers, thus the beam was assumed to be uniform in the axial direction.

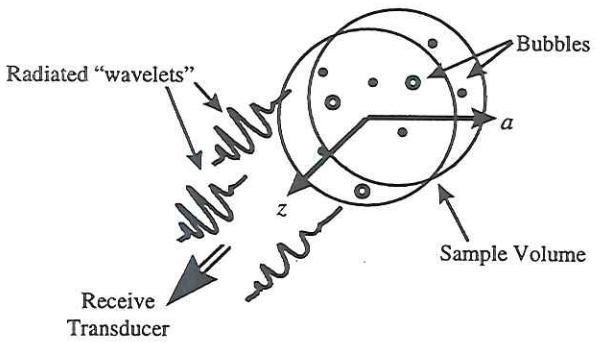

Figure 2: *In response to the local incident amplitude, each bubble in the sample volume contributes a "wavelet" to the received waveform.*

Results: Two-cycle pulses at 1.4, 2.9 and 5.8 MHz were used as incident waveforms. For each pulse several hundred time-domain responses for different bubble radii and incident amplitudes were generated. In figure 3 we plot the data for 2.9 MHz in a novel way as maps of fundamental and second harmonic cross-sections, that is, energy radiated within a frequency band per unit incident intensity. These maps allow one to quickly visualize the relative significance of bubble size and incident amplitude.

Ensemble echoes were calculated for a range of incident focal amplitudes. From the time-domain echoes, the powers received by the transducer at fundamental and second harmonic frequencies were calculated and plotted in figure 4. In the fundamental band, the power received is approximately proportional to the square of incident amplitude, but a slight saturation effect can be observed above 100 kPa. In the harmonic band, the power received has a more complicated dependence on incident amplitude. For 1.4 and 2.9 MHz, the power law exponent (slope on the log-log plot) ranges from a maximum of 3.75 ± 0.15 to about 2.8 ± 0.3 at incident amplitudes above 200 kPa. At 5.8 MHz, the maximum slope reached only about 3.0 at 200 kPa. While these result are derived from a focused disc transducer, simular dependence of harmonic response on frequency can be expected for other transducer geometries, including arrays.

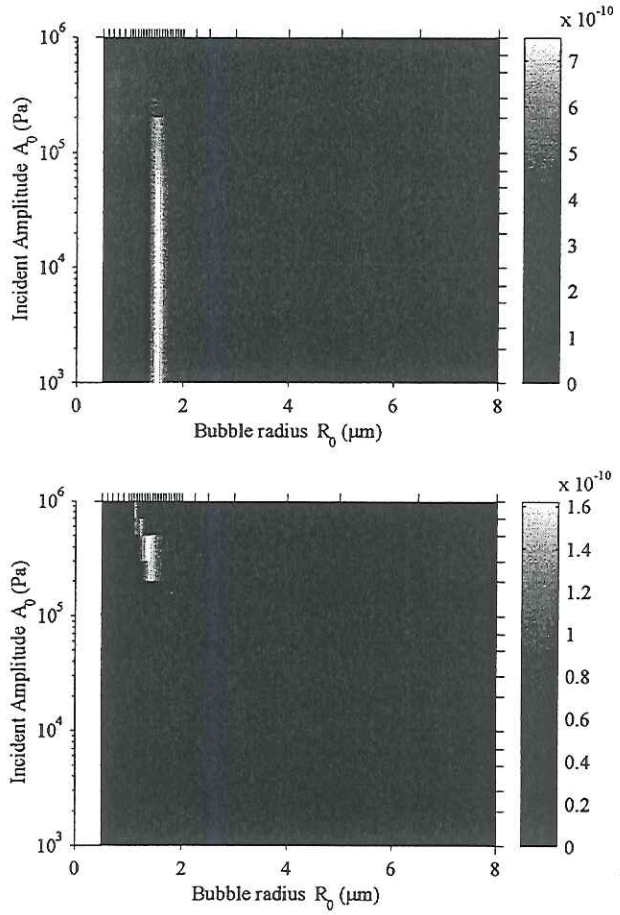

Figure 3: *Fundamental and second harmonic responses of single bubbles to the 2.9 MHz pulse. Gray level represents linearly the cross-sectional areas in* m^2.

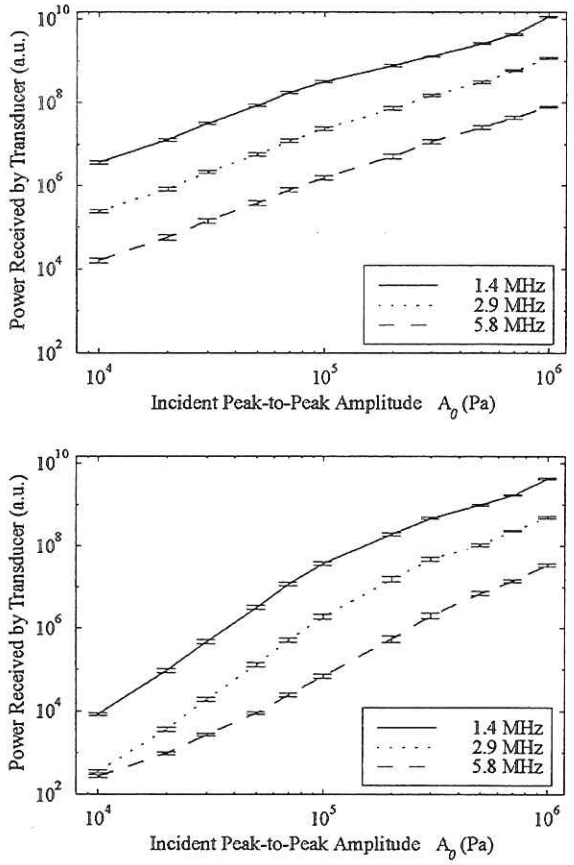

Figure 4: *Fundamental and second harmonic responses of simulated agent as a function of incident focal amplitudes at three frequencies. The error bars represents standard error of the mean calculated from 32 independent random ensembles.*

Significance: We have developed a new model of contrast agent response to a real ultrasound beam. Individual bubble behaviour is illustrated with scattering cross-section maps which provide useful insight into the interaction bewteen bubble nonlinearity and beam shape. Looking at figure 3, one can observe a strong resonance at about 3.0 μm diameter for f_0 = 2.9 MHz and the response is essentially independent of incident amplitude up to about 100 kPa. Above 100 kPa, nonlinear effects set in to broaden the response, reduce the resonant size and reduce the peak cross-section. The reduction of fundamental cross-section is due to a transfer of energy to higher harmonics. Thus, in the second harmonic cross-section one can see the gradual increase towards a maximum at about 500 kPa from the same resonant bubbles. Near 1 MPa, so much energy is transferred to the higher harmonics that even the second harmonic cross-section is reduced. Therefore, the model predicts that there is an amplitude that maximizes the second harmonic to fundamental ratio. Above this optimal amplitude, second harmonic efficiency deceases as higher harmonics become more significant. Preliminary experiment in our laboratory appear to substantiate this observation for the agent DMP115 (Dupont Merck). Note that this prediction applies to stable bubbles and is

independent of the reduced scattering caused by bubble destruction. This model also helps explain the effective sidelobe suppression that harmonic imaging can offer under certain conditions. For example, if the amplitude is 300 kPa at beam centre and 60 kPa at the highest sidelobe, then a study of figure 3 would suggest that the bubbles in the sidelobe will contribute a fractionally smaller amount of energy to the harmonic signal than to the fundamental signal. Again, this improvement is dependent on focal pressure amplitude. This provides a possible explanation for the improved image quality in harmonic imaging in spite of its reduced axial resolution.

By combining single bubble echoes into a time-domain signal that realistically reflects the bubble distribution and the incident and receive beams, we believe we have cleared the major theoretical hurdle towards an experimentally verifiable model to test new agents and new imaging strategies. We believe this theory is suitable for the simulation of images and the development of nonlinear bubble detection techniques. Benchtop measurements that can verify the presented theory, in particular the dependence of the power relationship between harmonic response and incident amplitude on frequency, are currently in progress. Future work includes the addition of a thermal damping process to the single bubble equation, and the use of a complete impulse response for the transmit and receive beams.

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A NEW MULTI-PULSE AND DECORRELATION-DETECTION STRATEGY FOR IMPROVED ULTRASOUND CONTRAST IMAGING

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Introduction: With the advent of ultrasound contrast agents, new *ad hoc* imaging modalities have been and continue to be developed. These techniques are designed to improve the sensitivity of ultrasound imaging systems for bubble detection by exploiting specific "acoustic signatures" of the contrast agents (e.g., Harmonic B-mode and Harmonic Power Doppler).

Of special relevance is the particular signature that occurs at high acoustical power settings. The scattering increases dramatically due to the nonlinear behavior shown by encapsulated-gas types of contrast agents, e.g. Quantison™ (Andaris Ltd., Nottingham, UK) and Sonovist® (Schering AG, Berlin, Germany). It has been shown that free gas bubbles are released as the encapsulating shells are ruptured by a high power ultrasound field[1]. The result is an enhancement of the scattering (ES) and the duration of the effect is related to the survival time of the free gas bubbles in the medium. This particular signature has been addressed by several names: Acoustically Stimulated Acoustic Emission (ASAE), Power Enhanced Scattering (PES), Flash Imaging, Acoustic Scintillation, etc.

In conventional B-mode imaging, ES may be visualized as bright echogenic areas. However, in hyperechoic regions or very small vessels this increase in echogenicity can be masked by echoes from surrounding tissue. In Doppler imaging, the change in echo signal associated with gas release is construed as motion and demonstrated by a colored mosaic map, an approach termed loss-of-correlation (LOC) imaging[2]. With Harmonic Doppler imaging, the signal to clutter ratio is increased further[3]. There is, however, an inherent tradeoff between contrast and imaging resolution due to the narrow band character of Doppler detection and of harmonic imaging. Furthermore, ES can only be efficiently utilized in ECG triggered imaging because the contrast agent would be rapidly depleted at normal frame rates. This becomes particularly important in low or zero flow conditions (perfusion imaging, static contrast agent).

With the current imaging techniques, contrast agent disruption (gas release) and imaging are achieved during the early part and late part of a relatively long (several cycles) burst, respectively. However, it has been reported that the process of releasing gas bubbles is more efficient at lower frequencies, for a given number of cycles per burst and a fixed amplitude. It also improves with

longer acoustic pulses of fixed amplitude and frequency[4], while imaging resolution improves at high frequencies and short pulses. In this paper, we describe a method that resolves this situation by separating the "release" and "imaging" processes. As a result, high resolution imaging can be achieved with optimum utilization of the contrast agent.

The Multi-Pulse Decorrelation Approach: We propose a new contrast imaging approach based on the combination of a) a multi-pulse strategy and b) temporal decorrelation based detection. Multiple "imaging" pulses are used to survey the target before and after the disruption of contrast agent by a high power "release" burst (Figure 1). The change in echo signal arising from areas occupied by contrast agent is detected by temporal decorrelation analysis. The power required to disrupt the agent and release free gas bubbles is agent dependent and within the capabilities of commercial ultrasound imaging systems. Other multi-pulse schemes can be designed for specific purposes.

Local decorrelation analysis is performed on small (one wavelength) sliding radiofrequency signal windows to obtain decorrelation profiles along the beam direction. Decorrelation detection performs well at high bandwidths, contrary to Doppler detection. Only areas where released gas is present will show significant decorrelation. A decorrelation threshold of 80 % was defined empirically in order to differentiate tissue from contrast agent rich areas. An example is shown in Figure 2, where the measured correlation falls below the threshold level only within a region occupied by released gas. High decorrelation regions are displayed by superimposing a color-coded map on the original B-mode image, analogous to duplex imaging combining color Doppler and B-mode.

*Experimental method:*A number of experiments were performed to verify the feasibility and potential of the proposed approach. Initial experiments were conducted in a small water tank to characterize the ES of the agent. Two single element, broadband transducers were mounted perpendicularly. One to transmit two low amplitude, single cycle, 5 MHz pulses. The second one to transmit a narrow-band (4 cycles), high amplitude, 2 MHz burst.

We also performed measurements on test objects consisting of fibers (200 μm to 2 mm) embedded in agar blocks. Small carborundum (SiC) scattering particles were mixed with the agar to mimic high echogenic surrounding material. A Quantison™ (air bubbles encapsulated by a shell of human albumin) solution, similar to clinical settings, was introduced in the fiber. Finally, we performed corresponding test experiments using a standard ultrasound imaging system in B-mode and Doppler modes.

*Results :*In this abstract, we only describe the results of the 200 μm fiber experiment (Figure 3). To emulate a triggered M-mode representation, the imaging echo lines are depicted as gray-scale coded bars. These can also be construed to be lines of a hypothetical image. Figure 3A shows five independent echo lines obtained without the high power burst, i.e., the scattering of the intact Quantison™. Figure 3B shows echo lines after the multi-pulse sequence, but without decorrelation

detection. Although an increase in scattering from the released air bubbles is expected, the small fiber is difficult to locate within the highly echogenic surrounding material. Finally, Figure 3C shows the result of the multi-pulse decorrelation approach. The location and size of the fiber are accurately depicted.

Discussion and Conclusion: Separation of the bubble rupture and imaging processes, and decorrelation-based detection yields a powerful combination of resources that results in simultaneous high resolution imaging and optimal use of the contrast agent. Note that, in the reported experiment, high resolution detection could not have been achieved with a long, low frequency pulse and that bubble release could not have been easily achieved with a short, high frequency pulse. Thus, the synergy of the combination approach is responsible for the successful outcome.

The power and duration of the release burst can be designed to optimize the amount, and perhaps the type, of free gas bubbles released. This, in turn, translates into a longer period of imaging per unit amount of contrast agent, or alternatively in a lower dose of contrast agent required for imaging. Additionally, optimized agent usage can reduce attenuation caused by the contrast agent itself and thus improve imaging penetration. Due to the sensitivity of the decorrelation approach, as few as two signals can be used to detect the released gas (as demonstrated in the example herein). However, more than two signals can be used to obtain improved decorrelation estimates.

Due to the independence of bubble release and imaging processes, the multi-pulse decorrelation method has the potential to achieve high resolution, sensitivity and efficient contrast agent imaging heretofore unavailable.

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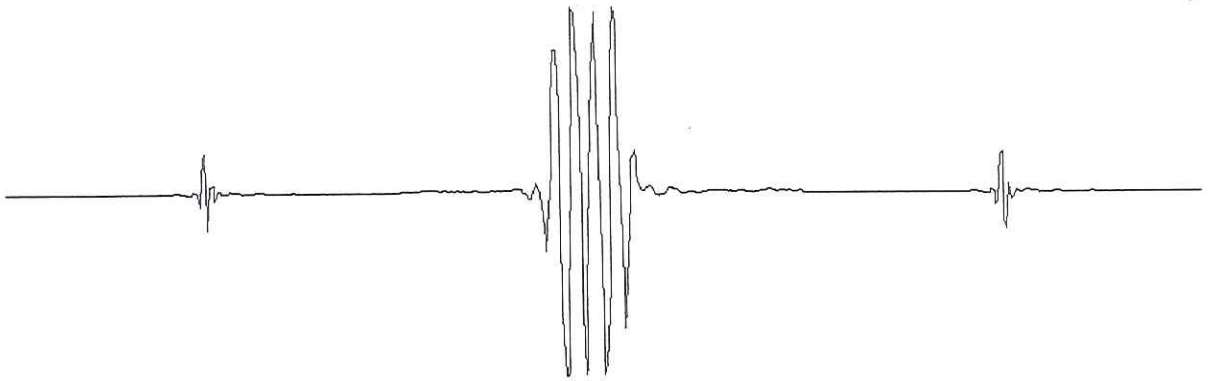

Figure 1. A typical multi-pulse sequence consisting of two low amplitude, single cycle, 5 MHz "imaging" pulses and one high amplitude, four cycles, 2 MHz "release" burst.

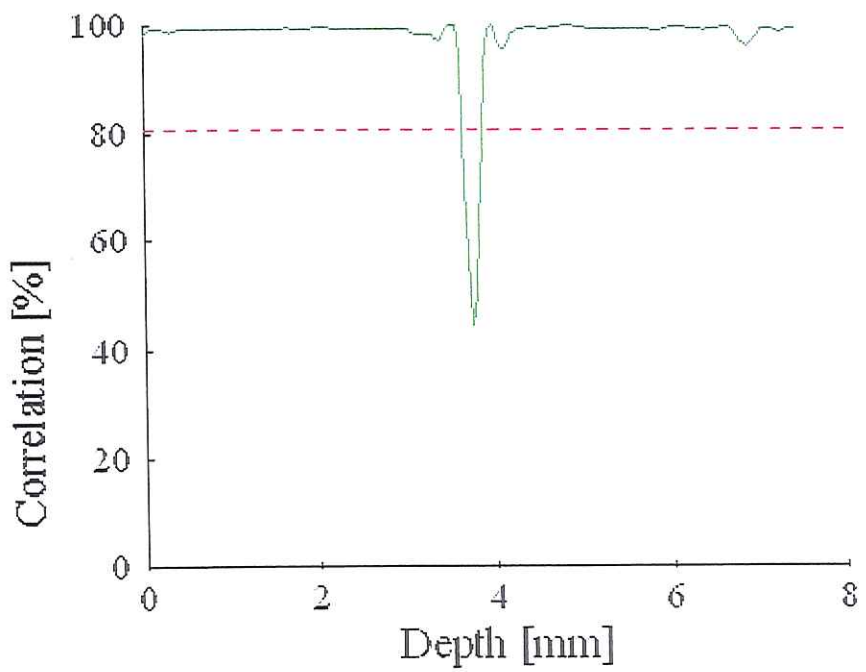

Figure 2. Decorrelation profile obtained from a single multi-pulse sequence. Thresholding the data, for example using a 80% correlation level, allows the detection of the area of bubble release.

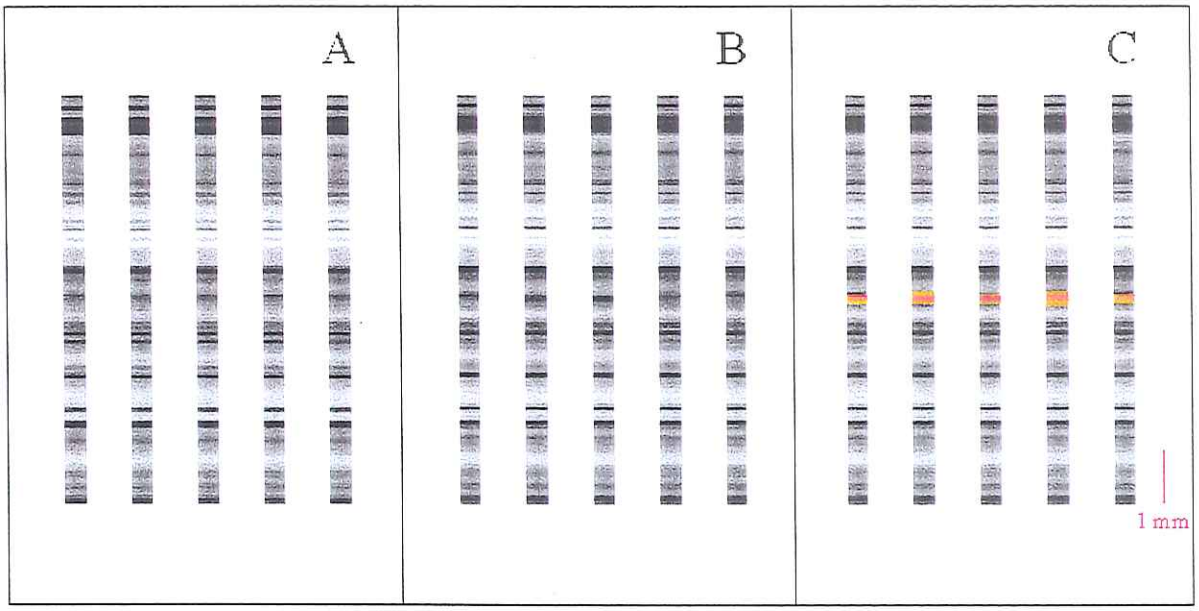

Figure 3. Triggered M-mode representation of a test object containing a single fiber filled with Quantison™ (five realizations). The total depth is 7.5 mm and the fiber is 200 μm in diameter. A) 5 MHz M-mode representation (one echo line per bar) without the high power burst; B) The high power burst is switched on, notice that gray scale enhancement can hardly be detected; C) Same as B but decorrelation detection and display: the colored area corresponds well with the size of the fiber. These five measurements can be used independently or combined to represent a single image line.

PULSE INVERSION DOPPLER: A NEW NONLINEAR IMAGING METHOD FOR MICROBUBBLE CONTRAST AGENTS

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Background: Almost all clinical applications of ultrasound contrast agents rely on, and are limited by, our ability to detect and image microbubbles in the presence of tissue.

Harmonic power Doppler and harmonic colour Doppler are the most sensitive techniques currently available for detecting and imaging microbubbles in tissue. They both use harmonic detection which exploits the fact that, unlike tissue, microbubbles are highly nonlinear scatterers of ultrasound. In harmonic detection, sound is transmitted into the body at one frequency, f_o, and the received echoes are filtered at the second harmonic $2f_o$. Linear scattering from tissue produces echoes only at f_o which are suppressed, while nonlinear scattering from microbubbles produces echoes at $2f_o$ which are detected.

Harmonic detection involves an inherent tradeoff between contrast and imaging resolution (Figure 1): if the transmit pulse bandwidth (centred about f_o) and the receive bandwidth (centred about $2f_o$) overlap, then the linear echoes from tissue will be detected in the harmonic signal. Such echoes reduce agent to tissue contrast and can mask the nonlinear echoes from small quantities of agent, especially at low incident intensities when nonlinear scattering is weak. To increase contrast, the transmit and receive bandwidths must be narrowed, degrading axial resolution. This tradeoff currently limits both the sensitivity and resolution of harmonic imaging techniques, particularly insituations where in situ concentrations of agent or incident sound intensities are limited. Because of its reduced sensitivity at low transmit intensities, harmonic imaging is commonly performed at high transmit intensities where microbubble disruption is rapid and imaging frame rates must be reduced significantly to maintain detection sensitivity. The power dependent contrast of harmonic imaging also leads to variations in detection sensitivity with depth and transmit focus. Finally, the resolution of harmonic detection limits its ability to detect and resolve small vessels, such as those supplying the myocardium and those found in tumours.

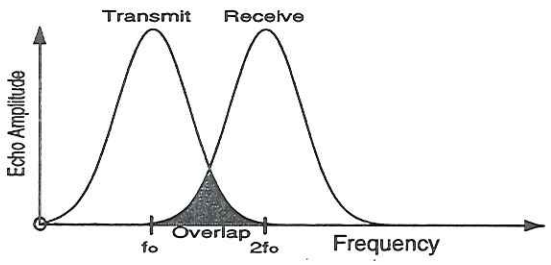

***Figure 1**:Overlap between the transmit and receive bandwidths results in unwanted signal in harmonic mode.*

We have developed a technique for detecting nonlinear scattering from microbubbles, called pulse inversion Doppler, which overcomes the contrast/resolution tradeoffs of harmonic imaging techniques.

In pulse inversion Doppler, a series of ultrasound pulses are transmitted at a fixed pulse repetition frequency (*PRF*). Unlike conventional Doppler, every second transmitted pulse is inverted. The received echoes are demodulated by mixing them in quadrature with a carrier at a frequency f_c, typically chosen either near the centre of the transducer passband (for broadband transmit pulsing), or at the second harmonic of the transmit frequency (for narrowband transmit pulsing). The demodulated signals are then processed using conventional PW Doppler processing to produce a Doppler spectrum.

This simple scheme allows linear echoes from tissue to be separated from nonlinear echoes from microbubbles, even if both are moving at the same velocity. For linear scattering, inverting successive transmit pulses causes the detected Doppler signals to be modulated at a rate equal to half the Doppler pulsing frequency. The linear Doppler shift frequency, $f_{d,linear}$, will thus be:

$$f_{d,linear} = \frac{2v}{c} f_c + \frac{1}{2} PRF \qquad (1)$$

where v is the axial velocity of the scatterer relative to the transmitter, c_s is the speed of sound.

For nonlinear scattering, echoes can be decomposed into odd and even components as follows:

$$\begin{aligned} Echo\{+\} &= e_{even}(t) + e_{odd}(t) \\ Echo\{-\} &= e_{even}(t) - e_{odd}(t) \end{aligned} \qquad (2)$$

where *Echo{+}* represents an echo from a normal transmit pulse and *Echo{-}* represents an echo from an inverted transmit pulse. For successive echoes, the $e_{odd}(t)$ component changes sign with the transmitted pulse, but the $e_{even}(t)$ component doesn't. This decomposition is general and does not depend on the exact nature of the scattering process.

The Doppler shifts due to these two components are:

$$f_{d,odd} = \frac{2v}{c} f_c + \frac{1}{2} PRF$$
$$f_{d,even} = \frac{2v}{c} f_c. \qquad (3)$$

Note that $f_{d,even}$ has a Doppler shift identical to that produced by conventional Doppler.

Providing all scatterer velocities obey a revised Nyquist limit:

$$\frac{2|v_{max}|}{c_s} f_c \leq \frac{1}{4} PRF, \qquad (4)$$

which is half of the conventional limit, the portion of the Doppler spectrum between *-PRF/4* and *PRF/4* will contain only Doppler signals arising from nonlinear scattering processes. The remaining half of the Doppler spectrum will contain Doppler signals arising from both linear scattering and nonlinear scattering (Figure 2).

For colour and power Doppler imaging, Doppler frequencies greater than *PRF/4* can be removed using suitable filters, and all existing spectral estimation techniques can then be applied.

Since pulse inversion Doppler separates nonlinear scattering from linear scattering not by echo frequency (as with harmonic Doppler) but by apparent Doppler frequency shift, it can function over the entire bandwidth of the echo signal, thus achieving superior spatial resolution in the Doppler image.

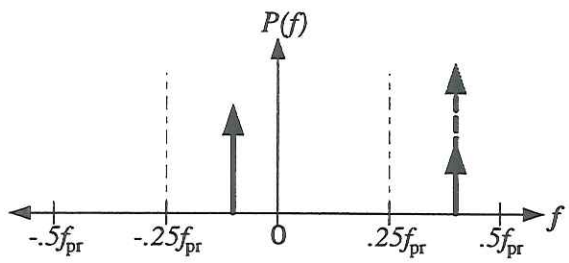

Figure 2: *The pulse inversion Doppler spectrum separates linear scatterers (dotted line) from nonlinear scatterers (solid lines) moving at the same velocity.*

Figure 3 shows sample results from in vitro experiments comparing flowing contrast agent (Sonovist, Schering AG, Berlin) and linear-scattering cellulose particles. Such experiments confirm theoretical predictions and suggest that pulse inversion Doppler can provide 3 to 10 dB more agent to tissue contrast than harmonic imaging with similar pulses. This improvement in contrast is greatest at low incident sound pressures (Figure 4).

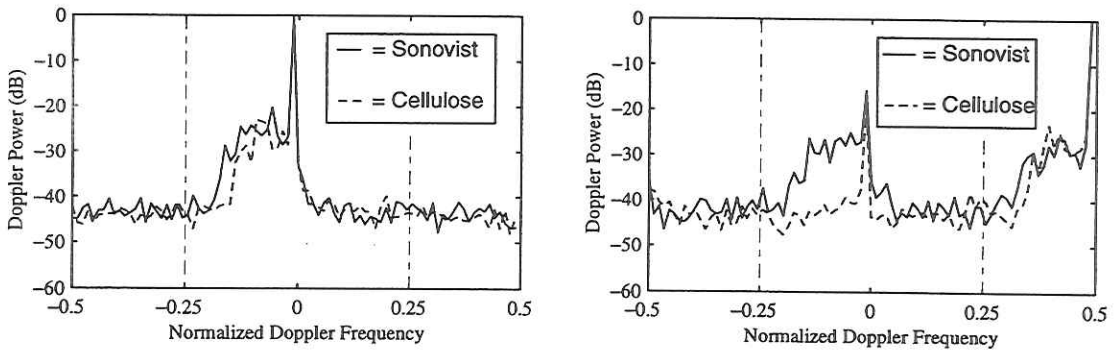

Figure 3: Harmonic Doppler (top) and pulse inversion Doppler spectra (bottom) from Sonovist and cellulose measured under similar conditions (fixed agent concentrations and receiver gains, 5 cycle transmit bursts at 120 kPa peak to peak). Doppler frequencies have been normalized to the PRF. The spectra show improved contrast in the nonlinear portion of the spectrum.

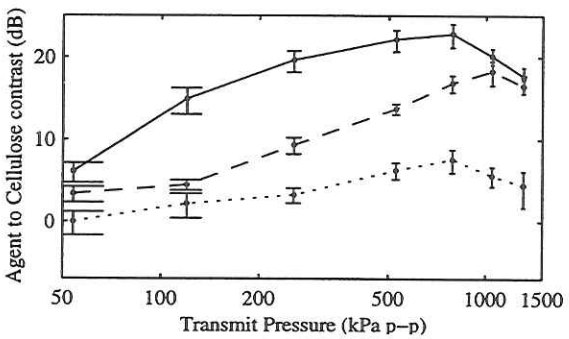

Figure 4: Sonovist to cellulose contrast vs transmit pressure for 5 cycle transmit bursts. Lines represent conventional (dotted), harmonic (dashed) and pulse inversion Doppler (solid). Pulse Inversion Doppler provides more contrast than harmonic Doppler, especially at low transmit intensities.

Similar experiments suggest that broadband (high resolution) pulse inversion Doppler can provide up to 16dB more contrast than broadband conventional Doppler (harmonic detection provides almost no benefits for broadband pulsing).

Significance: Pulse inversion Doppler is a sensitive, high resolution ultrasound technique for separating linear and nonlinear scattering. It provides motion discrimination capabilities similar to conventional Doppler techniques and has a maximum detectable Doppler shift which is half that of conventional Doppler. Although further testing is required, results from *in vitro* experiments show that it can offer three significant benefits over harmonic Doppler, the most sensitive technique currently available. These benefits are: greater resolution, higher sensitivity, and improved performance at low transmit levels.

There are a number of implications for contrast ultrasound imaging strategies based upon this technique. Due to its increased resolution, nonlinear colour Doppler imaging is possible at high resolution, improving the delineation of small vessels. Due to its improved sensitivity, smaller quantities of agent will now be detectable. A lower dose of agent can be used for a specified task, and a given dose of agent can provide more contrast and a longer effective imaging time. Due to its improved performance at low power levels, it should provide more robust contrast throughout the image field of view. Pulse inversion Doppler imaging can also be performed at lower transmit intensities, prolonging microbubble lifetimes and reducing the need for intermittent imaging techniques. Together, these factors should enhance the capabilities of contrast ultrasound imaging in applications ranging from myocardial perfusion measurement to tumour diagnosis and staging.

One final application deserves special mention. Harmonic greyscale imaging is now being used to image "tissue harmonic" echoes in the absence of contrast media. These echoes are generated by nonlinear propagation of the transmitted pulse followed by linear scattering from tissue and appear to improve image quality in some patients. Pulse inversion Doppler can be operated in a high frame rate power imaging mode in which as few as two pulses of sound are transmitted down each line of sight. This could offer a "tissue harmonic" imaging technique operating at half the frame rate of harmonic greyscale imaging but with higher resolution and contrast. While analysis shows that contrast with the two-pulse imaging technique will be degraded by tissue motion, a four or six pulse version should be more robust and could be used (at a reduced frame rate) in applications such as echocardiography where motion is an issue.

References:

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2. [1] Averkiou MA, Roundhill DN, Powers JE. A New Imaging Technique Based on the Nonlinear Properties of Tissues. *Proceedings of the IEEE Ultrasonics, Symposium*, 1997, in press.
3. *Proceedings of the IEEE Ultrasonics, Symposium*, 1997, in press

MICROBUBBLE ENHANCED DYNAMIC HEPATIC DOPPLER VENOGRAPHY - A PROMISING NOVEL TECHNIQUE FOR THE NON-INVASIVE DIAGNOSIS OF LIVER CIRRHOSIS.

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Background: So far US has been of little value in the differential diagnosis of diffuse liver disease and in particular in the diagnosis of (compensated) cirrhosis which is largely the domain of liver biopsy. However cirrhosis goes hand in hand with a number of haemodynamic changes which - provided an appropriate Doppler technique to detect these were available - could aide the sonographic diagnosis of cirrhosis. These haemodynamic changes are:(1) reduction of the portal venous hepatic blood supply resulting in arterialization, (2) portal to hepatic venous intrahepatic shunt formation, (3) intrapulmonary arterio-venous shunt formation and (4) a hyperdynamic circulatory state.

Hypothesis: All these haemodynamic changes should result in an earlier arrival of a iv injected microbubble bolus in the hepatic veins of cirrhotics in comparison to normals with a different dynamic enhancement profile.

Purpose:(1) To assess whether dynamic measurements of the spectral Doppler intensity of a hepatic vein can be used to measure changes in the first pass of a iv injected microbubble bolus and (2) to explore whether such measurements are helpful in the differentiation of different types of diffuse liver disease.

Methods: To date 36 individuals have been included: 10 healthy volunteers with normal livers, 13 biopsy proven cirrhotics (5 x Child A, 6 x Child B, 2 x Child C) and 13 biopsy proven cases of non-cirrhotic diffuse liver disease (mostly chronic hepatitis B or C and alcoholic steatohepatitis). None of the subjects had focal lesions and all were fasted for at least 5 hours prior to the study. Continuous spectral Doppler US of a hepatic vein (mostly middle) was performed from 20s before to 3min after an iv bolus injection of 2.5g Levovist (Schering AG, Germany) in the antecubital fossa. The Doppler gain was standardised and continuous Doppler intensitometry was performed using the acoustic out

put of the scanner which was imported into a PC with in-house software. Time-intensity curves were plotted using the raw data as well as exponentially smoothed data (which provided less noisy traces) and analysed for the following parameters: Start time (defined as the interval between the injection time and the first point of the raw data curve that was clearly above the baseline and followed by a further rise of the signal), Time to peak, absolute peak (in multiples of the baseline intensity) and the rise rate; the latter 3 indices were derived from the smoothed data

Results: The time intensity curves obtained from the cirrhotics were markedly different from those of the normals and of the patients with non-cirrhotic diffuse liver disease. While all cirrhotics showed an early and very steep rise after a mean start time of 18 s, all normals and non-cirrhotic patients showed a later and much more gradual rise after a mean start time of 52 and 39 s respectively. A watershed of <24 s for the start time provided 100% separation of the cirrhotics from the normals and non-cirrhotics. Cirrhotics also had a higher mean peak enhancement than the two other groups (58.3 units vs. 12.4 and 12.7 units, $p<0.005$) as well as a shorter time to peak (53 s vs. 78 and 101 s, $p<0.005$) and a higher rise rate (1.25 /s vs. 0.17 and 0.17 /s, $p<0.005$). No significant differences were found between normals and patients with non-cirrhotic disease.

Conclusion: Our novel technique of dynamic Doppler analysis of microbubble first pass of the liver provides clinically useful functional information about the haemodynamic changes in liver cirrhosis. In our small pilot series an arrival time of the microbubble bolus of less than 24 s was 100% sensitive and specific for liver cirrhosis. This promising new functional imaging tool may enable us to diagnose liver cirrhosis non-invasively and thus reduce the number of liver biopsies in the future.

A NEW STRATEGY FOR IDENTIFYING CONTRAST AGENT ECHOES

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Hypothesis: The order of compressional and rarefactional half-cycles in the transmitted pulse affects the time and frequency domain characteristics of the received echo from an ultrasound contrast agent. We hypothesize that these effects may be exploited to differentiate bubble and tissue echoes, and thus present a study of the echoes from individual microbubbles as a function of the transmitted phase.

Methods : A unique system is used that allows both optical and acoustical observation of contrast agent microbubbles flowing through a phantom vessel. This system consists of two perpendicular transducers mutually focussed on 200-micron diameter cellulose tubing that is at a 45° angle to the two transducers. One transducer is used to transmit pulses at a center frequency of 2.25 MHz (Panametrics V305) and the other receives the signals scattered from the bubbles in the vessel using a center frequency of 5 MHz (Panametrics V309). The phantom is also coupled to a microscope for optical viewing of the microbubbles. The transmitted pulses are generated using an arbitrary waveform generator (Tektronics AWG2021) and then amplified using a RF power amplifier (ENI 325LA). The bubble echoes are received using a broadband receiver (Ritec BR-640). The peak negative transmitted pressure was approximately 700 kPa. These experiments utilize a very low concentration of a contrast agent suspended in saline, on the order of 1 sphere/• L, and our experimental system with small diameter tubing produces a contrast-filled sample volume of approximately 0.04 • L. Similar results have been obtained with several agents, but the results presented here are obtained using MP1950, an experimental agent (Mallinckrodt, Inc., St. Louis, MO) that has a phospholipid shell and a decafluorobutane core.

The transducer is excited by single cycle pulses with a phase of 0° (compressional half-cycle followed by rarefactional half-cycle) and a phase of 180° (rarefactional half-cycle followed by compressional half-cycle). The echoes received from single bubbles were recorded from more than 200 transmissions for each phase. The received echoes from pairs of transmitted pulses separated by approximately 3 microseconds (as shown in Figure 1) were also recorded. Approximately 50 echoes were evaluated for each of the following three transmission sequences; both pulses with 0° phase,

the 0° phase followed by 180° phase, and 180° phase followed by 0° phase. Using this data, both time and frequency domain characteristics are evaluated. We also compare echo recordings with optical images of variations in the bubble radius during insonation of microbubbles tethered to a polystyrene plate.

Results: The effect of transmitted phase on the frequency spectrum and time domain envelope of bubble echoes is now summarized. The mean frequency of the bubble echo is lower when the 0° case is transmitted. Specifically, when the 0° case is transmitted, a mean frequency of 3.9 MHz is observed, while a mean frequency of 4.3 MHz is observed when the transmitted pulse has a phase of 180°. In addition, the 0° case often results in a longer time domain envelope.

Table 1 shows that the time interval between the first major rarefactional peaks of the two received echoes corresponds to the time interval between transmitted rarefactional peaks. The mean received time intervals are summarized, together with the time intervals for the transmitted pulses as measured by a hydrophone. The results show a dependence of the received echo timing on the rarefactional half-cycles. Specifically, if the time between transmitted rarefactional half-cycles is decreased, as in the 0 - 180° phase case, the time measured between the received rarefactional peaks decreases proportionally. Our preliminary results suggest that the significant portion of the bubble echo coincides with the first major rarefactional half cycle of the transmitted signal.

Transmitted phase combination	Transmission: Time between first major rarefactional peaks in a pulse pair (microseconds)	Received echoes: Time between first major rarefactional peaks in a pulse pair (microseconds)
0 - 0	2.95	2.94
0 - 180	2.72	2.70
180 - 0	3.16	3.20

Table 1. Time interval between the first major rarefactional peaks in each pulse pair on transmission and reception

In Figure 2, echoes from individual bubbles insonified by pairs of pulses are shown, including two echoes received following the 180 - 0° transmitted phase combination and two echoes received following the 0 - 180° transmitted phase combination. Note that the echoes resulting from each

transmitted phase are similar in all cases. The magnitude of the correlation between successive bubble echoes will be further detailed in our presentation. We thus demonstrate that for very short transmissions, the time domain envelope from a single bubble echo is predictable, and hypothesize that bubbles can be recognized by correlating received echoes with a bubble echo prototype.

With our optical system, we are currently unable to measure fluctuations in bubble radius during these short pulses. As a first effort to optically document fluctuations in bubble radius, a continuous-wave insonation is used, and the resulting oscillations will be presented. The mean bubble radius is measured before and during insonation and the results are used to better understand the effects of compression and rarefaction.

Conclusion: Characteristics of bubble echoes, including the mean frequency, duration and time domain signature, change with the transmitted signal phase and demonstrate a high correlation between successive echoes. Transmission of several signal phases may be an important component of strategies to identify bubbles in vivo.

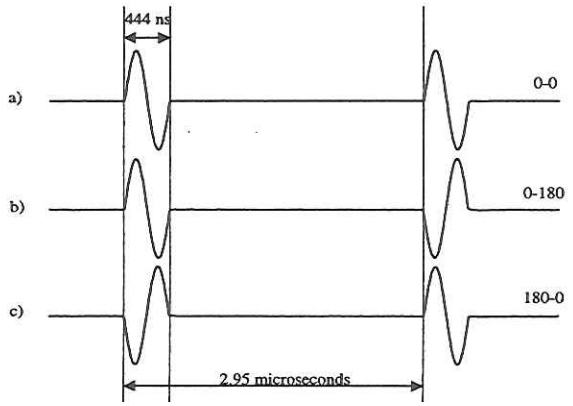

Figure 1. Transmitted signals used to excite the wideband transducer. 1a, two identical pulses with compression followed by rarefaction, 1b, pulse pair with compression followed by rarefaction in the first pulse and rarefaction followed by compression in the second pulse, 1c, pulse pair with rarefaction followed by compression in the first pulse and compression followed by rarefaction in the second pulse

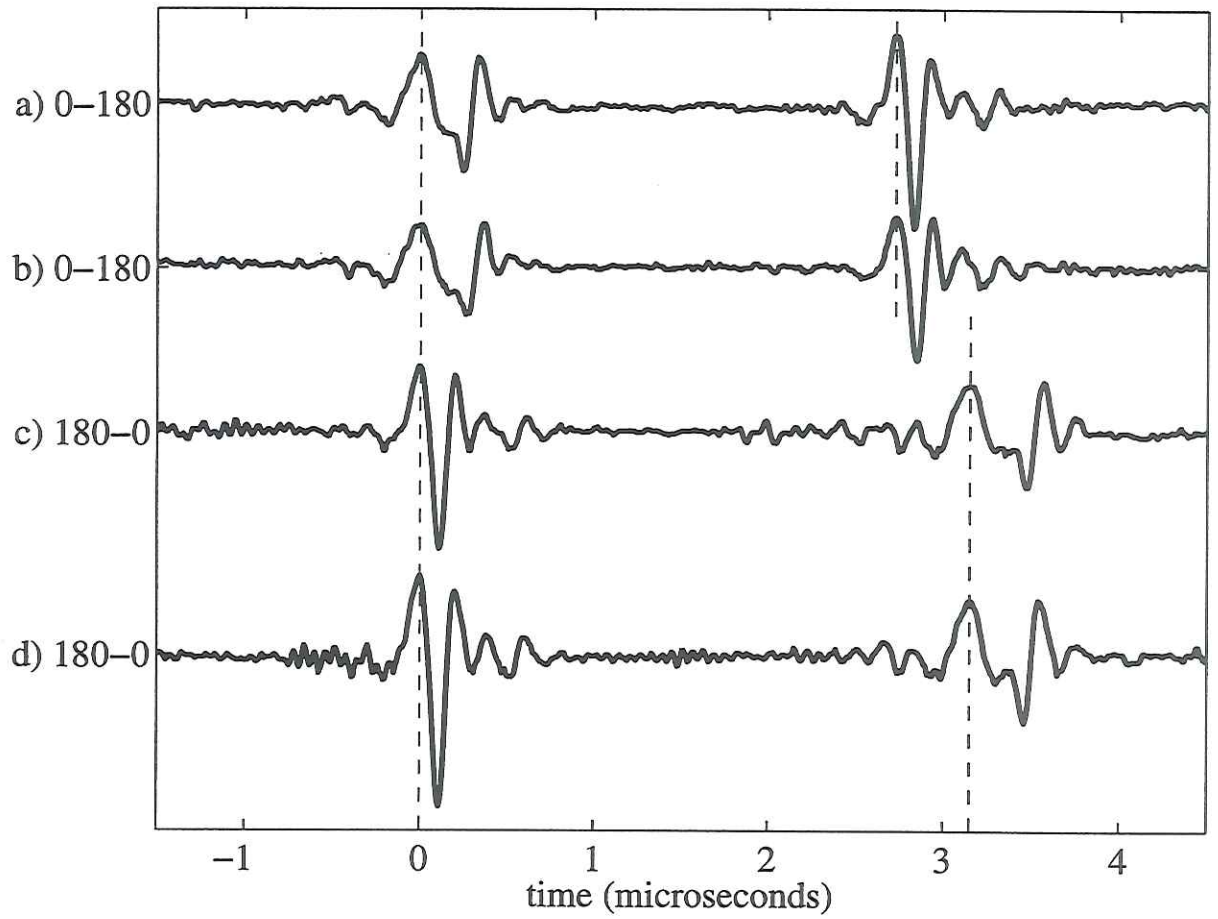

Figure 2. Received echoes from individual bubbles demonstrating the results of changes in the transmitted phase. 2a and 2b, examples of the 0 - 180° transmitted phase combination 2c and 2d examples of the 180 - 0° transmitted phase combination. The first compressional peak has been aligned between the two cases, in order to facilitate a comparison of the echo timing.

VASCULAR ECHOGENICITY WITH CONTRAST MATERIAL AND HIGH RESOLUTION HARMONIC IMAGING: EFFECTS OF VELOCITY, CONTRAST CONCENTRATION, AND PULSE REPETITION FREQUENCY.

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Purpose: *In vivo* vascular imaging using ultrasound contrast material and high-resolution harmonic (HRH) imaging demonstrated that it was possible to differentiate arteries from veins based on vessel echogenicity. This experiment further explores this observation under controlled, *in vitro* conditions.
Methods: A tissue-mimicking flow phantom circulated gas-equalized water with contrast material utilizing either constant or pulsatile flow. Velocity was varied from 1-100 cm/s while microbubble concentration (Imagent® US, Alliance Pharmaceutical Corp., San Diego, CA) was varied from ¼ to 2 times diagnostic dose. Pulse repetition frequencies (PRF) from 200-1600Hz were evaluated at each velocity and concentration of contrast material. Echogenicity measurements were performed with images acquired with both 7.5 and 3.5MHz transducers using a prototype Siemens Elegra (Siemens Ultrasound, Issaquah, WA) equipped for HRH imaging. The impact of flow velocity, contrast concentration, and PRF on image enhancement was evaluated.
Results: Vascular echogenicity increased with increasing contrast concentration, increasing flow velocity, and decreasing PRF. In pulsatile flow, the echogenicity exhibited cyclic behavior with echogenicity greatest during maximum velocity (systole) and least during minimum velocity (diastole). Overall enhancement and differentiation of systolic and diastolic flow was dependent upon PRF selection and imaging frequency.
Conclusion: This high resolution harmonic imaging technique displays images with echogenicity that is sensitive to contrast concentration, flow velocity, and PRF. *In vivo*, the echogenic enhancement resulting from the greater velocity and pulsatility of arterial flow provides the ability to visually differentiate arterial and venous vessels. Maximal vascular differentiation is dependent upon the PRF selection.

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CONTRAST APPLICATIONS FOR DIGITAL WIDE BAND RF OUTPUT.

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The System 5 from Vingmed Sound AS has been equipped with a Radio Frequency (RF) output capability. This feature enables the storage of RF data to disk for post processing. The RF data is written to disk in complex base band form. The data is stored in EchoPAC format, and hence provides a vehicle of exchange between the different Vingmed processing and visualisation platforms.

Vingmed has also developed EchoMAT, a Matlab based software processing package, providing the user with direct access to the RF data. In addition to gaining access to the data, EchoMAT contains numerous signal and image processing tools such as scan conversion, filtering and densitometry. The user is presented with the RF data at his fingertips in addition to the processing power needed to perform a series of interesting operations. Furthermore, great care has been taken in writing EchoMAT so as to simplify the extension of the package to incorporate new Matlab files. This possibility may significantly enhance the power of the package.

The presentation will give an overview of the RF options on the System 5. In particular, it will provide an explanation of the main difference between the narrow and wide band options.

A brief introduction to the EchoMAT software package will also be presented. Two examples will be covered, both based on recordings of a closed chest dog after injection of the Nycomed NC100100 contrast agent.

The first example considers the filtering of the wide band RF signal to obtain 2^{nd} harmonic images. This is a built-in feature of EchoMAT and illustrates what may be achieved with the package in its unmodified form.

The second example broaches the problem of the estimation of perfusion time constants in the myocardium. This is a non-standard feature of EchoMAT and is included to illustrate the considerable potential involved in handling and processing RF data off-line.

HARMONIC FLASH ECHO IMAGING

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Microbubbles in a diagnostic ultrasound field can be induced to nonlinear motion. Ultrasound emitted by microbubbles contains harmonics at double the frequency of transmitted ultrasound. Second harmonic system would be extremely useful in detecting tissue perfusion. However, it is well known that the insonification of ultrasound induces the destruction of the microbubbles and affects the contrast enhancement. The conventional harmonic method diminishes the effect of enhancement by the contrast agents.

We found a very large echo signal like a flash was obtained for the first transmission of ultrasound after several seconds' suspension. By succeeding transmissions, very weak signals were obtained because the microbubbles disappear after the first transmission. Flash Echo Imaging (FEI) has been developed to detect those transient echoes from the microbubbles effectively.

FEI is a new method which is based on the intermittent transmission and has the unique feature of a flexible ultrasound transmission control using the second harmonic method. First, it enables the acquisition of multiple successive frames at one trigger during the intermittent mode. It makes the detection of the dynamic change of the contrast enhancement easily. ' Monitor scan ' is another feature and enables to obtain both the real-time images at a low acoustic power level and the triggered image at a high acoustic power simultaneously. The intermittent transmission technique is very useful to obtain strong contrast enhancement. However, it also vitiates an advantage of ultrasound system, which is real-time observation. 'Monitor scan' would overcome this limitation. It helps the observation of the region of interest without much affection of the bubble collapse.

Flash Echo Imaging will allow to obtain an effectively enhanced image of tissue perfusion with the real-time observation. It will give a new capability of visualizing the perfusion of organ to ultrasound system.

CONTRAST QUANTIFICATION METHODS

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The current state of the art in ultrasound contrast imaging allows reasonably reliable detection of areas of significantly reduced or non-existent perfusion. However, the goal is to be able to measure more subtle reductions in perfusion, or flow characteristics that require more than a binary flow / no flow discrimination. Several techniques are being developed which promise to provide that capability.

The most widely discussed and investigated is that of indicator dilution methods in which a tracer is injected and its concentration measured downstream of the injection point. Then the time to peak and time to wash out is a measure of flow rate and the area under the curve is a measure of blood volume. This is widely used in the operating room where cold saline is injected in a Schwann Ganz catheter and the temperature measured with a thermistor at the end of the catheter. It is also being used with other imaging modalities and contrast agents. This technique has been used in ultrasound for the classification of breast lesions and renal perfusion abnormalities.

Indicator dilution techniques suffer from bolus spreading following an IV injection. This can make the measurement of slight changes in transit times difficult. For detection of more subtle stenoses, especially in the heart, a new technique has been suggested. This uses the well established fact that most microbubbles are destroyed by ultrasound. By destroying the microbubbles within the scanplane, and then waiting varying periods of time before scanning again, the time required to reperfuse the scanplane can be determined. This time constant gives an indication of severity of stenosis.

NATIVE TISSUE HARMOMIC IMAGING

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Native Tissue Harmonic Imaging is a new and important imaging modality providing significant clinical benefits in many applications. Here, the inherent capability of the body to generate signals in the harmonic frequency band is harnessed to form images. The advantage of using these signals over the fundamental signals propagating through the body will be explained. The clinical impact of Native Tissue Harmonic Imaging will be shown. Transmit pulse optimization and receive path optimization techniques to improve signal to noise ratios of the harmonic signal will be explained.

QUANTIFICATION IN CONTRAST ECHO

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It has been demonstrated that the relationship between microbubble concentration and video intensity is a non-linear function which empirically resembles an increasing exponential. However, it has also been shown that there is a range in which "linear" operation occurs, making quantification of number of microbubbles from video intensity possible1. There are still several problems with such an approach. The use of video intensity instead of acoustic intensity forces the user to live with the non-linear post-processing and compression algorithms which are used by equipment manufacturers to make images aesthetically pleasing. These non-linear transformations will vary from system to system and even on the same system if care is not taken to keep settings constant. Inconsistent answers will occur and comparisons between results will not be possible. The use of acoustic intensity (i.e., Acoustic Densitometry) aids in this area and increases the "linear" range of microbubble concentration as well as allowing proper baseline subtraction2 .

Another major problem which remains with quantification is contrast-induced attenuation. The amount of contrast agent through which an ultrasound beam passes will affect the beam's attenuation and, therefore, the contrast enhancement in different regions. In other words, the greater the number of microbubbles between a region of interest and the transducer, the greater the amount of attenuation and the lower the measured intensity enhancement from contrast in that region. For example, say the attenuation changes from 0.2dB/MHz/cm to 1dB/MHz/cm from the addition of a contrast agent. If the region of interest is 10cm away and the imaging frequency is 2MHz, the attention will change from 4dB to 20dB. This means that that area will have to have an increase of more than 16dB before any intensity enhancement is measured. To further confuse the issue, the contrast-induced attenuation is time-varying and varies throughout the image. Simulations have indicated that in the parasternal short axis view3, even without contrast in the left ventricle, there can be a decrease in backscatter in various regions of the contrast-perfused myocardium. This is partly due to the increase in attenuation in the myocardium from the agent.

What can be done to help the situation? First of all, certain views are more prone to attenuation than others (parasternal views vs. apical views). Secondly, using a continuous infusion of agent will allow proper titration of the amount of agent and will ameliorate the situation. Thirdly, microbubbles which have a better backscatter-to-attenuation ratio (i.e., are more efficient scatterers) will help as well. Finally, from an ultrasound manufacturer's standpoint, coming up with more sensitive detection techniques will aid quantification. Harmonic Imaging is a prime example of this because it allows the dosage to be lowered by a factor of 10 thereby improving contrast induced attenuation problems. There are several other possibilities for improved sensitivity, including a combination of Image Alignment/Subtraction and colorization4, Harmonic Angio, tissue texture analysis and frequency shifts from introduction of agent5. It is important to keep in mind that any technique will require a linear relationship with bubble concentration to be useful for quantification.

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HARMONIC AND SCINTILLATION IMAGINGS, AN HONEST ENGINEER'S APPROACH AND SOME NEW FINDING.

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GE-Yokogawa Medical Systems, Ltd., Hino 191 Japan.

Introduction: In our community one year is quite sufficient time for exotic new technologies move down to engineering standard technology. Our case is also in that range, and we made prototype harmonic imager for technical feasibility proof of our method, based on earlier experiences with our mimicking agent (1) as well as real agents. Followings are brief summary of our experiences and findings, some of which may be new or worth notifying.

Design Philosophy: "Do the minimum necessary" or "remain as simple as possible", is basis of our prototyping. We applied a sharp cut-off fundamental frequency band rejection filter at the receiver beamformer output (2), together with aperture apodization in transmission in order to optimize harmonic response. We first concentrated to improve harmonics B-mode picture, which would lead any further processing such as harmonic color, power and point Dopplers, etc.

Implementation And Optimization: Latest high-end to mid-tyer equipments are basically "all-digital" and are never available for one night bolt and nut and soldering iron modification for cut and try by pondering researcher. To overcome this burden, we put a bunch of high speed, wide bit-width D/A converters at beamformer output to resurrect the analog echo signal back, to which we apply a classic analog LC band-pass filter for harmonic selection. To optimize filter parameter, we used 3-gang variable air capacitor used in vintage vacuum tube short-wave radio receiver. Since there must be no distortion in this filter, semiconductor devices such as transistors or varactor diodes are intendedly rejected, and here the 3-gang air variable condenser performed perfect job in this high fidelity passive variable band-pass filter in circuitry development.The key finding is that we need minimum 5th to 6th order (=30 to 36dB/oct.) cut-off characteristics for acceptable fundamental band rejection to have clean harmonic image. However, steeper cut-off filter also have longer "tail" in its impulse response, carefull trade-off and compromization are necessary. The optimized filter was implemented using fixed cmponents only. We gained about 20dB or more enhancement of background to agent echo level difference from fundamental to harmonic.In transmission we applied

aperture apodization very carefully to optimize harmonic response rather than fundamental frequency response. For transmission and reception overall we have nearly 30dB visibility enhancement. However, actual visibility of the agent in harmonic mode depends also on its harmonic yield, which might be agent specific and insonification condition dependent.

Real World Scanning: In harmonic mode, background linear echogen is almost gone and very neat agent-only image appears, when low level insonification (like MI<=0.4) where propagation distortion of incident wave is not so much, is performed and the gas-release threshhold of the agent (for example FS069/Optison) meets with this. This is much unlike the "parametric" mode imaging (aliased as native harmonic mode or tissue harmonic mode, etc.) pictures needs much higher transmission level to induce sufficient propagation distortion for in-situ harmonic insonification. This method comes from marine sonar technology (called "parametric sonar") having years and years of history, and the situations are completely same. In scintillation mode, by using normal or harmonic power Doppler mode, almost same nature of image appears. It would be a good race for real usefullness in between harmonic-B and fundamental-scintillation (or harmonic Doppler/scintillation) modes. Author is still unable to judge this race, most probably we would need both together for Doctors' choice.In pulsed/point Doppler mode, if using contrast agent, spectrum broadening due to agent scintillation (=appear and disappear)(fig.1) would causes a big misreading in conventional / traditional Doppler measurement for flow velocity, volume, etc., especially for slow flows where the spectrum broadening might mask the real flow pattern. This must be very very carefully encountered in contrast agent application, which the author warned very recently (3).

Something Completely New: Above are the latest experiences of the bolt/nut/soldering-iron "honest" prototyping engineer, however, these would be sooner or later an engineering standard technology to be put into a handbook or like. In "contrast", following is my latest pioneering but premature experience that may be interesting for this community. Solid particles seem completely obsolified for contrast agent in front of microballoon / microbubble method, however, for labeling methodology, bubbles and balloons are only one family of possibility and choice. Possible other labeling means include sound emitter in form of self emission or externaly excited emission, or externally modulated echogenicity including Doppler and scintillation. Author here introduces an in-vitro experience on micron size ferromagnetic (soft-ferrite) micropowder suspended in a mildly viscous fluid (x5 times diluted Aquasonic(R)) for about 1% weight fraction, put into a ultra-thin rubber balloon (condom) and placed in water vessel or in agar phantom. In step with externally applied alternating magnetic field intensity gradient, a visible Doppler-shift in the particle echo is observed by conventional color flow imager (fig.2). It will be 100% good for feasibility proof of this concept. The ferrite

micropowder used here is fairly within several micron in size, although its distribution is not so beautiful. Magnetic particle, or biological origin magnetite embedded in liposome, has been discussed for prospective contrast agent by Unger 's patent (4), however, external magnetic excitation of the agent is neither spoken nor discussed there. The method proposed here develops a novel concept of externally excited contrast echography, however unfortunately, the safe methods for introducing, locating, metabolization and/or rejection of such magnetic microparticle, to biological bodies, are not yet completely known.

Conclusion: In prototyping of harmonic imager, analog circuitry quick cut and try approach was much flexible and successful for honest bolt/nut/soldering-iron engineer, rather than manupirating in digital domain only. Steep fundamental cutoff filter in reception and prudent aperture apodization in transmission allowed nearly 30dB enhancement of relative visibility of the agent in harmonic B-mode picture. In modest insonification level, real time agent-only neat images were obtained. On the other hand, a novel concept of externally excited magnetic particle for contrast agent has been proposed with successful feasibility experiment.

Acknowledgement:

Author thanks greatly Drs. Sanjiv Kaul, Kevin Wei, Andre Linka, Howard Dittrich, Yigal Greener, Harold Levene, Fuminori Moriyasu, Hiroshi Kanai, Kai Thomenius, Anne Hall and Tai Bao Li, for their each intangible important assistances or contributions for this study.

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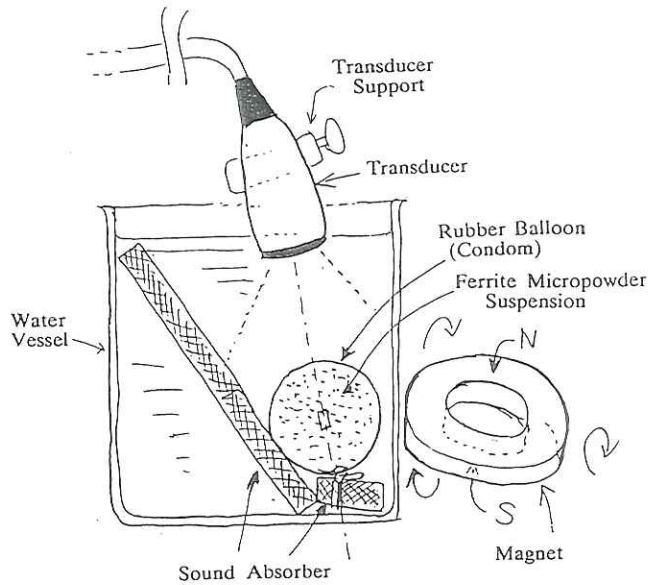
4. E. C. Unger, U.S.Pat. 5,088,499., patented Feb. 18, 1992, filed Aug. 20, 1990.

Fig.1 Schematic sketch of the method proposed here in this paper.



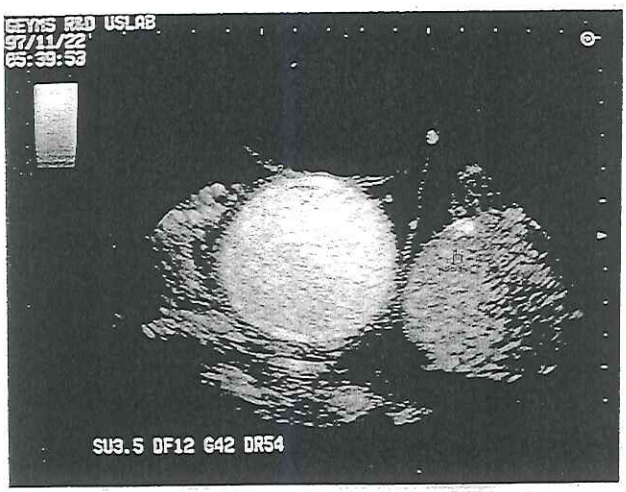


Fig.2a B-mode image of the ferrite micropowder suspension in mildly viscous fluid (=x5 diluted Aquasonic®). Right (darker) ball is mirror ghost of the left (brighter) one, due to vessel wall.

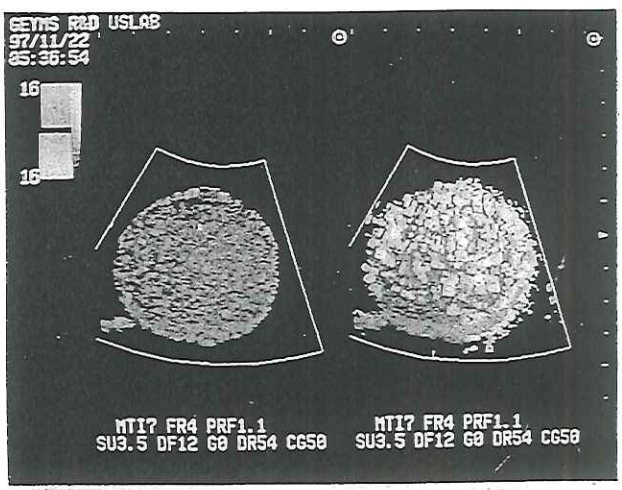


Fig.2b B+CFM mode images of the ferrite micropowder suspension, when externally applied magnetic field is stationary (left) and changing (right). (B/W representation of the color image)

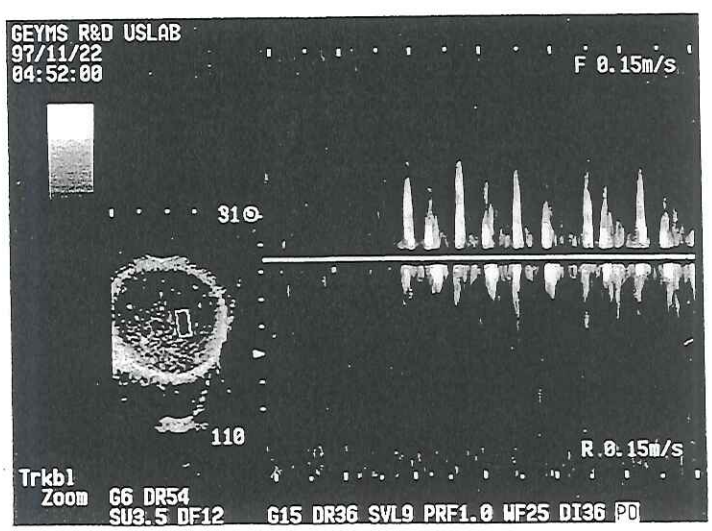


Fig.2c Point/pulsed Doppler observation of the moving particle in step with up/down of the magnet outside the water vessel.

6. A

SURVEY OF POTENTIAL PATHOFYSIOLOGICAL AND PHYSICAL PRINCIPLES FOR THERAPEUTIC DELIVERY OF DRUGS.

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The endothelial layer is now recognized as an important regulator of vascular homeostasis. Known as one of the first changes in the onset of atherosclerosis, endothelial dysfunction probably plays a role in various vascular disease states. This is characterized by for instance impaired vasorelaxation (NO), hyperpermeability (endothelial retraction) and leucocyte adhesion (adhesion molecules). These phenomena, in principle deleterious in nature, can however be put to good use.

Encapsulated gas bubbles with an albumin, liposome or polymeric shell can be directed towards the dysfunctional endothelium. By making use of the expression of adhesion molecules on the endothelial cells, the microbubbles can be made to adhere to, or linger in

areas with dysfunctional endothelium. Areas of endothelial dysfunction can thus be localized by making use of the echogenic properties of the encapsulated gas bubbles.

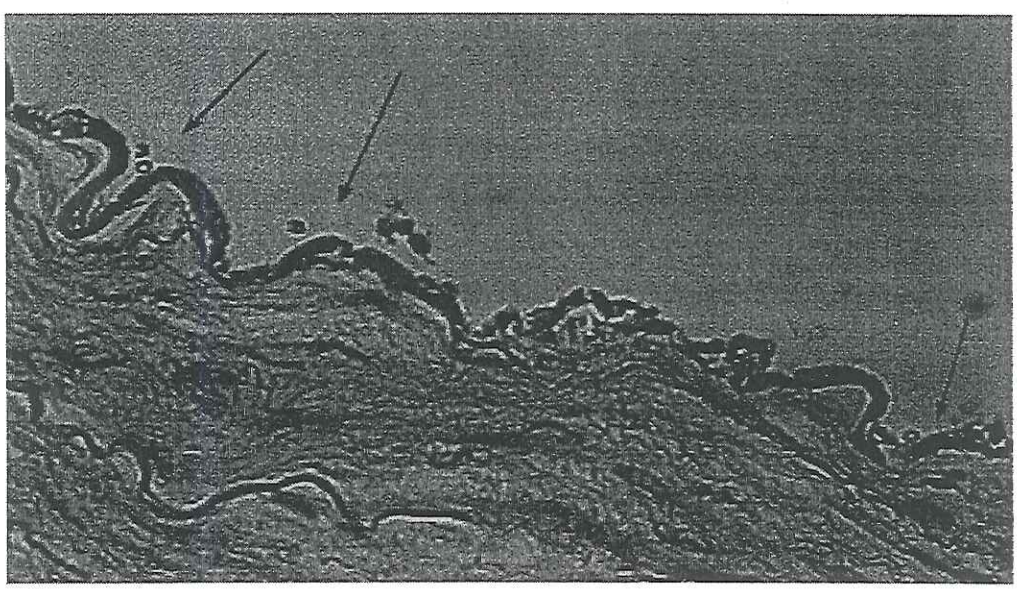

Fig 1: Albumin microbubbles adherent to activated endothelium. Hematoxylin Eosin stain, magn. 100X

A multitude of drugs can be coupled to microbubbles. By filling the spheres or by incorporating the drugs into the microbubble shell, the possibility for therapeutic intervention is created. Release of drugs can subsequently be controlled by ultrasonic techniques. The parameters that can dictate drug release are frequency, applied acoustic amplitude and duty cycle, alone or in combination.

Microbubble targeting and ultrasound directed drug release thus enables both the detection and treatment of vascular dysfunction. Its use could be further expanded to the treatment of regional myocardial dysfunction with local drug release in the microcirculation, without the restrictions of systemic pharmacological treatment.

HOW FAR FROM CLINICAL USE? ULTRASOUND-DIRECTED DRUG DELIVERY IN CLINICAL RADIOLOGY

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Several groups are developing new ultrasound contrast agents, which recirculate throughout the vasculature. New agents can also be targeted to selected areas such as thrombis. How might these new contrast agents be used for therapy and drug delivery? How far away are potential applications from clinical use.

The first application of ultrasound contrast agents in therapy will probably be for sonothrombolysis. Thrombosis is a very important clinical problem, and in industrialized countries, it may account for 50 percent of deaths overall, as well as substantial morbidity. Myocardial infarction and non-hemorrhagic stroke are to due to thrombus formation within an artery and blockage of arterial flow. Likewise, thrombosis is a significant problem in peripheral arterial vascular disease, deep venous thrombosis, and pulmonary embolism.

We, and others, have shown that microbubbles potentiate thrombolysis from ultrasound. The most effective regimen will probably involve application of ultrasound to the thrombus with concomitant thrombolytic therapy and microbubble agents (see Figure 1). The microbubbles probably lower the cavitation threshold in the clot and allow the enzymes (e.g., urokinase) to work more effectively for thrombolysis. Note that there is an effect of ultrasound alone with
thrombolytic therapy and that the microbubbles increase this rate of thrombolysis. Note also, that a thrombus-specific microbubble agent (e.g., Aerosomes MRX-408) has a larger effect than a non-targeted agent does.

Microbubbles may shorten the amount of time necessary for sonothrombolysis to restore blood flow. Microbubbles may also lower the requisite dose of thrombolytic drug (e.g. TPA). Reduction in the dose of thrombolytic can be very important clinically, as this may lower hemorrhagic complications. The shortening in time necessary for thrombolysis can reduce the amount of time of ischemia; this

doubtless will be important for salvaging myocardial and neurological tissue following myocardial artery occlusion or stroke.

Given the significance of potential applications for microbubbles in thrombolytic therapy, what will it take to develop these new applications, and how long will it take? Already several contrast agents are well along in clinical trials, and two agents have filed NDAs. Likely, the new agents used for thrombolysis will be given as an infusion. Agents, such as Aerosomes  MRX-115, which can be given as an infusion are sustained. Initially, the microbubble agents could be applied to the thrombus via a catheter approach with ultrasound administered either via the catheter or transcutaneously.

Clinical microbubble-enhanced sonothrombolysis could take as little as two years from now to develop. Once the new microbubble contrast agents are developed, off-label use could initially be performed for sonothrombolysis, but clinical trials will probably be necessary to optimize the use of these agents with ultrasound. Targeted thrombus-specific agents will improve sonothrombolysis. These new thrombus specific agents, however, will have to undergo clinical trials and therefore, probably would not be available for clinical application for several more years. Extensive applications for ultrasound-mediated drug delivery with acoustically active carriers are possible. A wide variety of diseases could be treated regionally or locally using microbubble based-carriers and ultrasound. Our own group has prepared a variety of different drugs in acoustically active carriers (see Table I). We have shown that stable drug carriers can be developed which are acoustically active, so that ultrasound can be used to "pop the bubbles" to locally release the agents. We have also shown that acoustically active materials can be used for gene delivery (see Figure 2). Applications such as gene delivery will probably take even longer to develop than some drug delivery applications. It will probably be several years until acoustically active drug carriers are developed. However, prior to the development of these agents, existing microbubble-based products (such as MRX-115) can be mixed with drugs for ultrasound-mediated delivery.

Model Drugs for Acoustically Active Carriers	Amphotericin B
Dexamethasone Prodrug	Urokinase
Dexamethasone	Vitamin E
Genes, Oligos, Antisense	Amphotericin B
Ribozymes	Taxol
GPIIbIIIa receptor ligand (RGD)	NSAIDs
	Insulin

NEW OUTLOOK OF SONOVUE™

A. Broillet, J. Puginier, R. Ventrone, M. Schneider

Bracco Research, Geneve, Switzerland

Many publications have shown that the second generation of ultrasound contrast agents generate reproducible myocardial opacification both in animals and humans when harmonic detection is combined with intermittent imaging.

Using intermittent imaging allows to reduce average acoustic pressure and thus microbubble destruction. However, thus technology does not allow to evaluate both wall motion abnormalities and perfusion defects.

We have shown in animal experiments with SonoVue™ injected intravenously that decreasing transmission power and frame rate to their minimal values allows significant and diagnostically useful myocardial enhancement during continuous imaging in both harmonic and fundamental modes (Fig 1).

Such results show that SonoVue™ holds promises for diagnosis of ischemic heart diseases in real time B-mode.

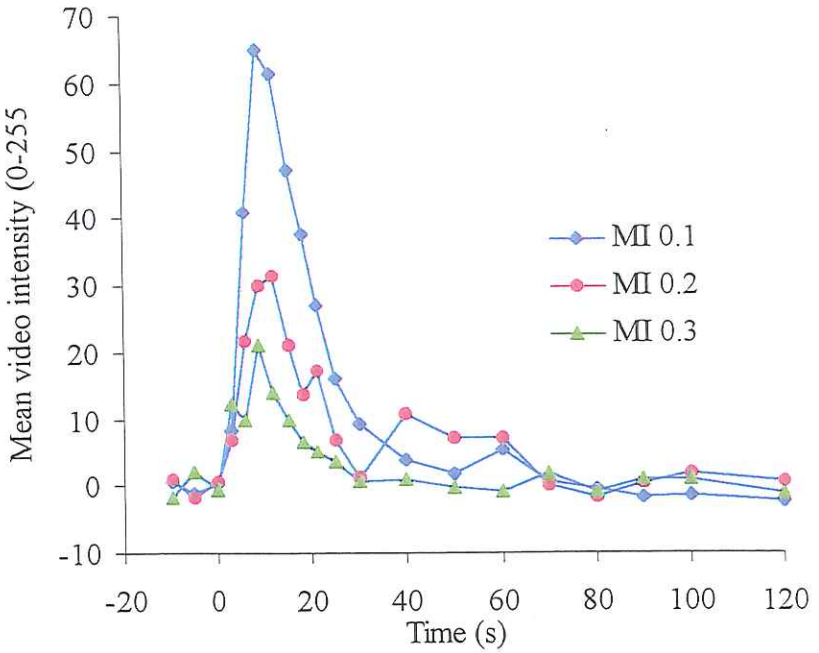

Fig 1. Effect of Transmit power (MI) on time-intensity curves obtained in the mini pig myocardium with SonoVue™ during continuous fundamental imaging:

CLINICAL RESULTS WITH NC100100

J. Østensen

Nycomed Imaging AS, Oslo Norway

The ultrasound contrast agent NC100100 (Nycomed Imaging AS) has been tested in clinical trials since 1996 after a preclinical period for optimalization of its acoustic and toxicological properties. These preclinical studies indicated very low attenuation and extremely low toxicity.

These properties were confirmed in humans in a placebo controlled Phase I study. Preliminary imaging results from Phase I showed enhancement of the normal human myocardium, large and small vessels, and of parenchymateous organs such as the liver. Dose finding studies have been performed for imaging of the myocardium in patients with ischemic heart disease. Additional studies are performed to collect data on the sensitivity and specificity for detection and evaluation of the extent of perfusion abnormalities in the heart.

These studies have shown that the best imaging modality of the human heart with NC100100 is second harmonic B-mode imaging. Technical studies are conducted to define the best approach for imaging of perfusion defects in the various regions of the heart as the anisotropy of the human heart represents a significant challenge especially for quantification of contrast enhancement. In addition to its many cardiological indications, NC100100 has shown excellent properties for many radiological indications.

Preliminary results indicate a significant improvement over unenhanced ultrasound for the detection and possible characterization of solid lesions in the liver. In these studies the advantage of a prolonged residence time in the liver is explored. Efficacy results from the various trials will be demonstrated.

THREEDIMENSIONAL MYOCARDIAL MASS

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Threedimensional myocardial mass determination has achieved considerable interest recently.

However the method is lampered by lack of optimal software and the availability of contrast agents with long persistence.

These problems may be overcome by use of 3D realtime imaging. However to visualize contrast agents an harmonic transducer is needed.

We developed a realtime 3D transducer which allows to measure myocardial mass in one heartbeat. The uniqueness of this transducer however is related to the possibility to analyze the pulsed ultrasound waves at a higher harmonic receiving frequency.

We will show the first in vitro and in vivo results of this new transducer using 3D harmonic for echocontrast imaging.

This development is a fundamental step forward in realtime 3D imaging by ultrasound.

IMAGING WITH LEVOVIST UTILIZING ACTIVE BUBBLE RESPONSE

A. Bauer, P. Hauff, M. Reinhard, M. Zomack, R. Schlief.

Schering AG, 13342 Berlin, Germany

Recent experience with Levovist have shown that diagnostic applications may go far beyond echoenhancement for previously failed Doppler examinations. Imaging the active bubble response of Levovist is facilitated with novel approaches to ultrasonic imaging and opens up new diagnostic opportunities.

With high amplitude Color Doppler and an ultrasound agent such as Levovist showing stimulated acoustic emission properties, the exposure to high power color Doppler generates a specific response: During a train of color Doppler pulses the signal intensity varies substantially. Stimulated acoustic emission causes uncorrelated signals generated by the bubble, and in the course of the insonation the bubble will be destabilized and lose its gaseous content. Both effects, acoustic emission and bubble destruction contribute to the visualized loss of correlation (LOC-) pattern. In short, this can be seen as the contrast agent inducing color Doppler signals by its acoustic response to high intensity ultrasound. The potential of LOC imaging with Levovist was evaluated in 5 volunteers. We could show a clear delineation of perfused liver parenchyma in all 5 volunteers during the blood pool phase of Levovist. The effects are limited to a small zone around the transmit focus, and are of short duration. No adverse events and no changes in hematology and enzymes occured during the study, confirming the excellent safety and tolerance of Levovist in this application.

A novel imaging technique, wideband harmonic imaging, is designed for the use with nonlinear ultrasonic contrast media. Wideband harmonic mode utilizes the full bandwidth of the ultrasound system on the receive side by applying two pulses, the first pulse is followed by an inverted second pulse and the sum of both is displayed. For the studies an experimental ultrasound system (Elegra, Siemens Medical Systems Inc., Issaquah, WA) was used, and second harmonic settings were compared to the wideband harmonic imaging within the same equipment. In vitro studies were performed in a water tank with a dialysis tubing to adjust the principal imaging parameters for Levovist. The optimized settings were investigated in rabbits and in dogs for imaging the liver and the kidney.

A high transmit amplitude (100%) was favourable for both, second harmonic (2,5MHz transmit, 5MHz receive) and wideband harmonic settings (2,5 MHz transmit, full receive bandwidth). In the beagle dogs, the contrast effect after Levovist injection was visible in all injections using wide-band harmonic. Delineation of the contrast filled areas (parenchyma vs gallbladder or urinary system) was clearly possible in all injections given. The sensitivity for Levovist could be improved by triggered imaging. With medium transmit amplitude (MI 0.1-0.5), the contrast filled areas were only incompletely visualized in second harmonic mode. With wideband harmonic at medium transmit amplitudes clear delineation of vessels and perfused parenchyma with almost no signals present at baseline was achieved. At highest transmit amplitude, the nonlinear response of tissue was apparently visualized in wideband harmonic mode in addition to contrast filled areas, which was less prominent in second harmonic mode.

Wideband harmonic imaging with Levovist is feasible and may be an improvement over conventional second harmonic imaging at low transmit power settings. At high transmit amplitudes, nonlinear tissue response may reduce the apparent image contrast between contrast agent and tissue. The adaption of ultrasonic equipment to contrast enhanced scanning and the utilization of nonlinear microbubble properties will impact the future diagnostic opportunities with ultrasound significantly.

* Wideband harmonic is a trademark of Siemens Medical Systems Inc. , Issaquah

+ Levovist is a trademark of Schering AG, Berlin

TWO CLINICAL CASES SHOWING THE USE OF INTRAVENOUS CONTRAST ECHOCARDIOGRAPHY USING BOTH FUNDAMENTAL AND HARMONIC IMAGING.

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Thoraxcentre, Rotterdam, The Netherlands.

Background: Recent developments in contrast agents and imaging techniques have brought the intravenous contrast echocardiography closer to practical applications. However, the imaging parameters must be tailored to achieve optimal visualization of the agent.

Clinical Illustration: The examples of intravenous contrast echocardiography will be presented demonstrating the clinical advantages of second harmonic imaging and appropriate transmit power setting:

Patient 1. An example of Levovist study in a technically suboptimal patient, aimed at optimized delineation of left ventricular endocardium.
Patient 2. An example of intravenous perfusion study using Quantison in a patient with coronary artery disease.

Conclusions: Efficient visualization of echocardiographic contrast agent is strongly dependent on the appropriate setting of an ultrasound system, according to the knowledge about the physical properties of a given agent.

TWO CLINICAL CASES DEMONSTRATING THE USE OF CONTRAST ECHO IN POSTMYOCARDIAL INFARCTION

O. Kamp

Department of Cardiology, Free University Hospital Amsterdam, The Netherlands.

New microbubble contrastagents cross the pulmonary circulation and permits evaluation of myocardial perfusion distribution within segments of the walls of the left ventricle.

Of thirty contrast echocardiograms performed in acute or subacute myocardial infarction, two patients are selected before, during and after intravenous injection of a contrastagent NC100100 (Nycomed®). In one case myocardial contrast echocardiography was performed between 5 and 10 days after myocardial infarction. It shows that despite wall motion abnormalities in this case myocardial perfusion distribution was completely normal. In another case with an acute myocardial infarction, a large perfusion defect will be demonstrated in a patient with a first anterior myocardial infarction. Twenty four hours after primary PTCA the perfusion defect is still present, however its size has been reduced. This patient had a primary PTCA with stent implantation. It confirms that perfusion defects can be present, even after opening of the infarct related vessel.

CORONARY FLOW IMAGING BY TRANSTHORACIC COLOR-DOPPLER ECHOCARDIOGRAPHY

P. Voci, A. Berni

Section of CardiologyII, " La Sapienza " University of Rome, Rome, Italy

Noninvasive imaging of segments of epicardial and transmural coronary arteries is feasible using a new, high-resolution ultrasound equipment.

We have studied 33 consecutive unselected patients (aged 43-70 years, average 55) in apical projections, to detect by color Doppler one or more segments of the middle-distal tract of left anterior descending coronary artery. Six patients had a previous myocardial infarction (1 anterior-septal, 2 apical, 3 inferior), 5 underwent coronary revascularization (4 coronary artery bypass grafting, 1 percutaneous transluminal coronary angioplasty), 2 mitral valve replacement with mechanical prosthesis, and 2 combined mitral and aortic valve replacement with mechanical prostheses. Five patients had systemic arterial hypertension, 6 mitral valve prolapse, 4 atrial septal aneurysm, and the remaining 8 subjects were normal.

Echocardiography was performed in the left lateral decubitus, by a multifrequency transducer allowing on-line change of frequency separately in 2D (3,5-7 MHz) and color-Doppler (3,5-6 MHz) imaging. The transducer was connected to an Acuson Sequoia C 256 (Acuson, Mountain View, CA) ultrasound system which utilizes multiple beam formers and coherent image former. This system provides a wide dynamic range and preserves both phase and amplitude data, with a high spatial and temporal resolution. To image the distal left anterior descending coronary artery, the transducer was placed either at the cardiac apex or one intercostal space upper, and focused on the proximal field. Once an optimal two-dimensional imaging of the apex and/or distal anteroseptal wall has been obtained, the transducer was rotated and tilted until one coronary segment and/or perforating branches could be visualized by color Doppler.

Color Doppler imaging was performed either conventionally, by reducing the Nyquist limit up to 12-20 cm/sec, or utilizing a special preset coronary program which displays only one color (yellow-red) to denote flows both towards and away from the transducer.

Blood flow velocity was measured by pulsed Doppler. The angle between the blood flow and ultrasonic beam has been optimized and adequately corrected, if necessary. Peak and mean flow velocity, as well as the deceleration time (msec) and deceleration rate (cm/sec^2), were measured on the diastolic phase of the Doppler tracing.

In 25/33 patients (76%) the middle-distal tract of the left anterior descending coronary artery was imaged by color Doppler. In 15 of 33 patients (46%) the periapical tract of the left anterior descending was imaged along with its perforating branches. In 2 out of 4 patients operated of coronary artery bypass grafting, the anastomosis between the left internal mammary artery and the left anterior descending coronary artery was imaged. In all 25 patients it was possible to measure by pulsed Doppler the coronary flow velocity pattern, characterized by a typical prevalent diastolic component. Peak diastolic flow velocity was 50 ± 17 cm/s and mean diastolic flow velocity was 37 ± 12 cm/s. The deceleration time was 916 ± 429 msec and the deceleration rate was 86.3 ± 69.3 cm/sec2. The Doppler pattern of the grafted mammary artery was different from the native mammary flow.

Recent advances in both ultrasound contrast agent and imaging technology, in particular harmonic color-flow Doppler imaging, will improve the feasibility of the technique and may allow a more complete imaging of the coronary arteries. The new contrast agents may also produce myocardial opacification, providing additional information on microvascular flow.

Some limitations affect this technique. The detection of coronary artery flow by transthoracic echocardiography requires a learning curve, and even experienced physicians may find difficult to maintain a constant projection throughout a stress test. Small angle variations may also affect velocity flow measurements. Finally, despite the periapical area is usually perfused by the left anterior descending, confirmation of the anatomic identity of the vascular structure is not possible. The operator should be aware that the apex may be in rare cases perfused by the right coronary artery, and that proximal segments of the anterior wall may be perfused by a diagonal branch.

In conclusion, this new non invasive imaging technique of the coronary arteries promises to expand the potentialities of echocardiography and brings new insight into the pathophysiology of ischemic heart disease.

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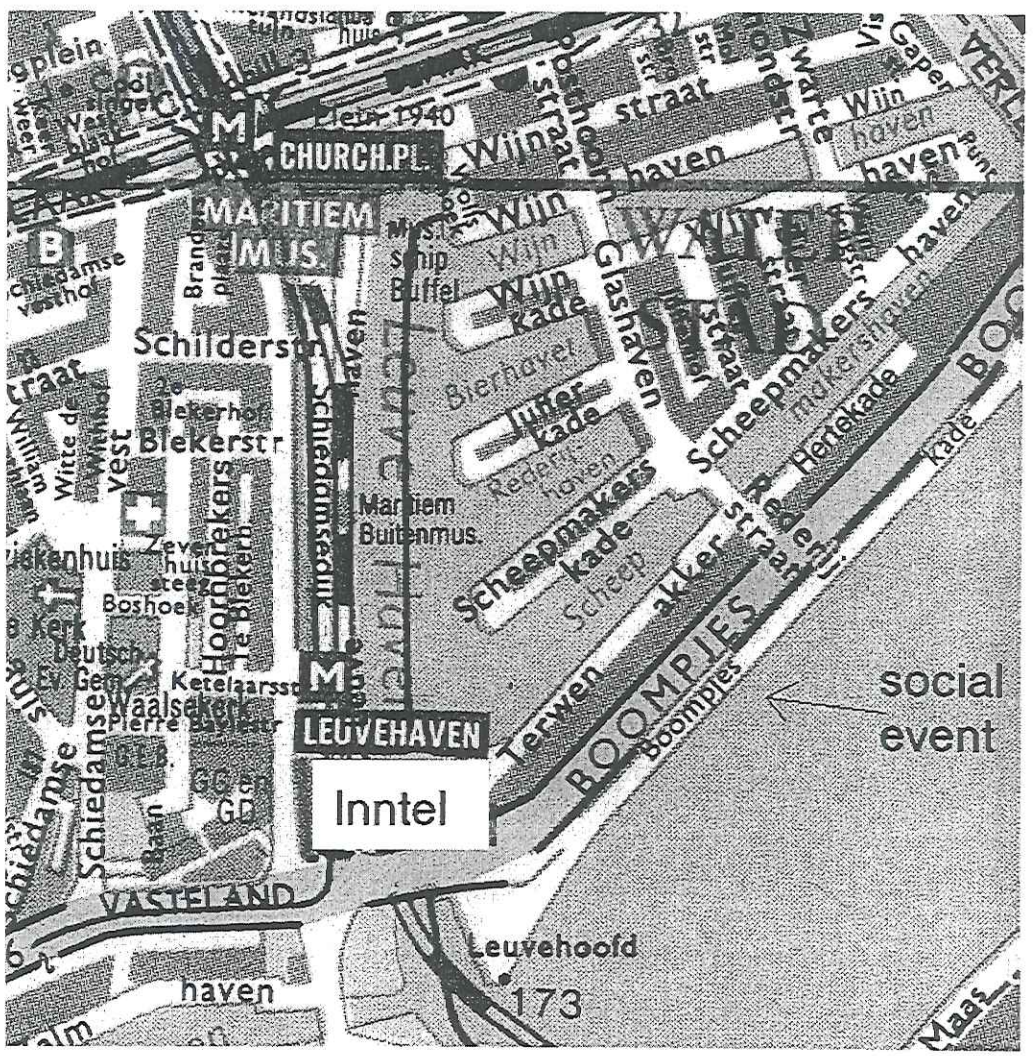

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FIRST ANNOUNCEMENT 1999:

4th THORAXCENTER EUROPEAN SYMPOSIUM ON ULTRASOUND CONTRAST IMAGING. 21 AND 22 JANUARY 1999, Rotterdam, The Netherlands.

Course Directors: Folkert Ten Cate and Nico de Jong
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Internet:http://www.eur.nl/fgg/thorax/contrast

Rotterdam, January 1998

4 TH ULTRASOUND CONTRAST SYMPOSIUM

20, 21 AND 22 JANUARY 1999

GENERAL INFORMATION:

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